

chain nodes :

15 16 17 19 20 21 22 24 25 26 27 28 35 37 39 42 43

ring nodes :

1 2 3 4 5 6 7 8 9 10 11 12 13

chain bonds :

15-16 15-17 17-19 20-21 20-25 21-22 24-26 26-27 26-28 37-42 39-43

ring bonds :

1-2 1-6 2-3 2-7 3-4 3-10 4-5 5-6 7-8 8-9 9-10 11-12 11-13 12-13

exact/norm bonds :

2-7 3-10 7-8 8-9 9-10 15-16 15-17 17-19 20-21 20-25 21-22 24-26 26-27 26-28 37-42 39-43

exact bonds :

11-12 11-13 12-13

normalized bonds :

1-2 1-6 2-3 3-4 4-5 5-6

isolated ring systems :

containing 1 : 11 :

G1:H,CH3,Et,n-Pr,i-Pr,n-Bu,i-Bu,s-Bu,t-Bu

G2:[\*1],[\*2],[\*3]

G3:H,CH3,Et

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom  
12:Atom 13:Atom 14:Atom 15:CLASS 16:CLASS 17:CLASS 19:CLASS 20:CLASS 21:CLASS 22:CLASS  
24:CLASS 25:CLASS 26:Atom 27:CLASS 28:CLASS 35:CLASS 36:Atom 37:CLASS 38:Atom 39:CLASS  
40:Atom 42:CLASS 43:CLASS

Generic attributes :

26:  
Saturation : Unsaturated  
Number of Carbon Atoms : less than 7  
Number of Hetero Atoms : 2 or more

Type of Ring System : Monocyclic

Element Count :

Node 26: Limited

C,C4

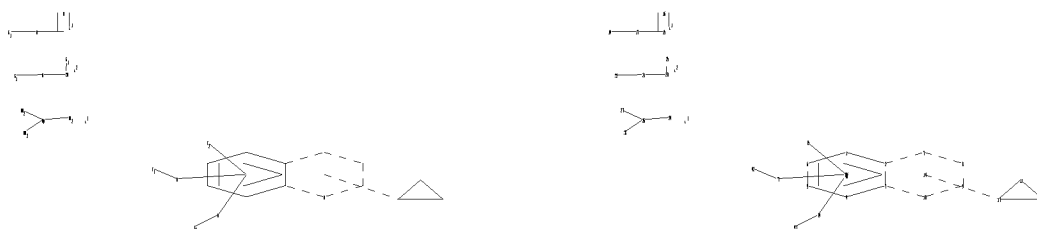
N,N2

O,O0

S,S0

=&gt;

Uploading C:\Program Files\Stnexp\Queries\10567558.str



chain nodes :

15 16 17 19 20 21 22 24 25 26 27 28 35 37 39 42 43

ring nodes :

1 2 3 4 5 6 7 8 9 10 11 12 13

chain bonds :

15-16 15-17 17-19 20-21 20-25 21-22 24-26 26-27 26-28 37-42 39-43

ring bonds :

1-2 1-6 2-3 2-7 3-4 3-10 4-5 5-6 7-8 8-9 9-10 11-12 11-13 12-13

exact/norm bonds :

2-7 3-10 7-8 8-9 9-10 15-16 15-17 17-19 20-21 20-25 21-22 24-26 26-27  
26-28 37-42 39-43

exact bonds :

11-12 11-13 12-13  
 normalized bonds :  
 1-2 1-6 2-3 3-4 4-5 5-6  
 isolated ring systems :  
 containing 1 : 11 :

G1:H,CH3,Et,n-Pr,i-Pr,n-Bu,i-Bu,s-Bu,t-Bu

G2:[\*1],[\*2],[\*3]

G3:H,CH3,Et

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom  
 11:Atom 12:Atom 13:Atom 14:Atom 15:CLASS 16:CLASS 17:CLASS 19:CLASS  
 20:CLASS 21:CLASS 22:CLASS 24:CLASS 25:CLASS 26:Atom 27:CLASS 28:CLASS  
 35:CLASS 36:Atom 37:CLASS 38:Atom 39:CLASS 40:Atom 42:CLASS 43:CLASS

Generic attributes :

26:

Saturation : Unsaturated

Number of Carbon Atoms : less than 7

Number of Hetero Atoms : 2 or more

Type of Ring System : Monocyclic

Element Count :

Node 26: Limited

C,C4

N,N2

O,O0

S,S0

L1 STRUCTURE UPLOADED

=> d l1

L1 HAS NO ANSWERS

L1 STR

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

Structure attributes must be viewed using STN Express query preparation.

=> s l1 sss sam

SAMPLE SEARCH INITIATED 16:36:58 FILE 'REGISTRY'

SAMPLE SCREEN SEARCH COMPLETED - 851 TO ITERATE

100.0% PROCESSED 851 ITERATIONS

1 ANSWERS

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*

BATCH \*\*COMPLETE\*\*

10/567,558

PROJECTED ITERATIONS: 15270 TO 18770  
PROJECTED ANSWERS: 1 TO 80

L2 1 SEA SSS SAM L1

=> => s l1 sss ful  
FULL SEARCH INITIATED 16:37:20 FILE 'REGISTRY'  
FULL SCREEN SEARCH COMPLETED - 17119 TO ITERATE

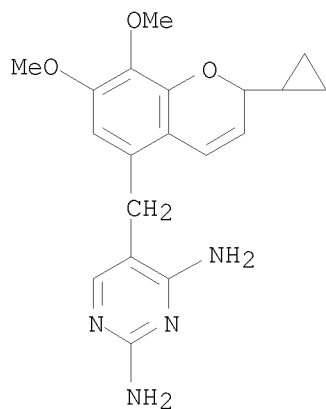
100.0% PROCESSED 17119 ITERATIONS 17 ANSWERS  
SEARCH TIME: 00.00.01

L3 17 SEA SSS FUL L1

=> => s l3  
L4 47 L3

=> d l4 1-47 bib,ab,hitstr

L4 ANSWER 1 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:1267885 CAPLUS  
 DN 151:398747  
 TI In vitro bactericidal activity of iclaprim in human plasma  
 AU Laue, Heike; Valensise, Tiziana; Seguin, Aurelie; Lociuero, Sergio; Islam, Khalid; Hawser, Stephen  
 CS Givaudan Schweiz AG, Duebendorf, Switz.  
 SO Antimicrobial Agents and Chemotherapy (2009), 53(10), 4542-4544  
 CODEN: AMACCQ; ISSN: 0066-4804  
 PB American Society for Microbiology  
 DT Journal  
 LA English  
 AB This study evaluated the effect of human plasma on the in vitro bactericidal activity of the novel diaminopyrimidine iclaprim against methicillin-susceptible and -resistant Staphylococcus aureus strains. MICs and minimal bactericidal concns. (MBCs) of iclaprim, with .apprx.93% protein binding, were similar in the absence and in the presence of 50% human plasma; MICs and MBCs ranged from 0.06 to 0.125 µg/mL. Furthermore, the activity of iclaprim was not affected by plasma, with ≥99.9% reduction in CFU after 5.0 to 7.6 h.  
 IT 192314-93-5, Iclaprim  
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (antibiotic activity of iclaprim in human plasma against Staphylococcus aureus)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:1262760 CAPLUS  
 DN 151:433924  
 TI Aqueous pharmaceutical formulation comprising  
 5-[(2RS)-2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-ylmethyl]-  
 pyrimidine-2,4-diamine methanesulfonic salt for bolus injection or i.v.  
 infusion  
 IN Gillessen, Dieter; Jaeger, Juergen  
 PA Arpida A.-G., Switz.  
 SO PCT Int. Appl., 35pp.; Chemical Indexing Equivalent to 151:433860 (US)  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 2

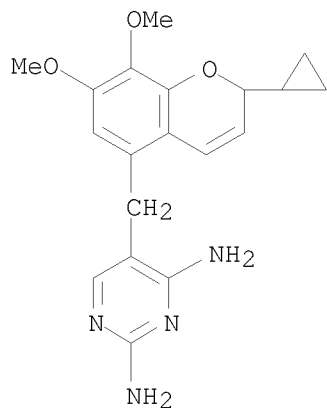
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009124586	A1	20091015	WO 2008-EP54232	20080408
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
US 20090253722	A1	20091008	US 2008-99284	20080408
PRAI US 2008-99284	T0	20080408		

# ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention concerns a stable aqueous pharmaceutical composition comprising 5-[(2RS)-2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-ylmethyl]-pyrimidine-2,4-diamine in form of the water soluble methanesulfonic acid salt, a physiolo. sodium chloride solution, ethanol and Povidone 12 PF, the liquid having a pH of over and above 4.8, but not higher than 5.2, and wherein the oxygen amount is controlled to be 0.8 ppm or less; which can be sterilized by filtration and/or by heated treatment, stored for longer time periods and which can be use for bolus injection or diluted for i.v. infusion.

IT 192314-93-5D, Iclaprim, addition salt 474793-41-4  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (aqueous pharmaceutical formulation comprising  
 5-[(2RS)-2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-ylmethyl]-  
 pyrimidine-2,4-diamine methanesulfonic salt for bolus injection or i.v.  
 infusion)

RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



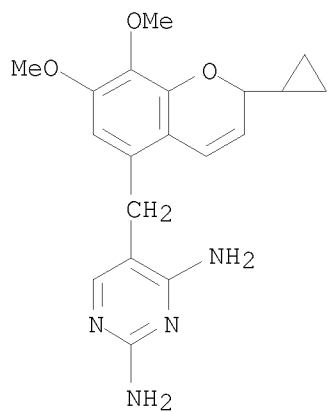
RN 474793-41-4 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 192314-93-5

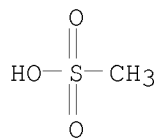
CMF C19 H22 N4 O3



CM 2

CRN 75-75-2

CMF C H4 O3 S





10/567,558

RE.CNT 4      THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:1228436 CAPLUS  
 DN 151:433860  
 TI Aqueous pharmaceutical formulation comprising  
 5-[(2RS)-2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-ylmethyl]-  
 pyrimidine-2,4-diamine methanesulfonic salt for bolus injection or i.v.  
 infusion  
 IN Gillessen, Dieter; Jaeger, Juergen  
 PA Arpida AG, Switz.  
 SO U.S. Pat. Appl. Publ., 10pp.; Chemical Indexing Equivalent to 151:433924  
 (WO)  
 CODEN: USXXCO  
 DT Patent  
 LA English  
 FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 20090253722	A1	20091008	US 2008-99284	20080408
	WO 2009124586	A1	20091015	WO 2008-EP54232	20080408
W:	AE, AG, AL, AM, AO, AI, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

PRAI US 2008-99284 T0 20080408

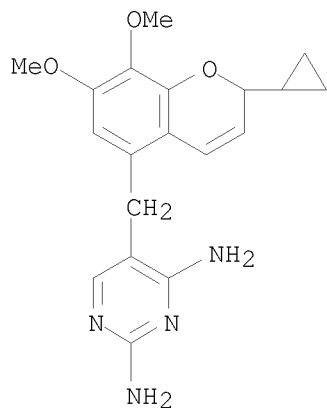
# ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention concerns a stable aqueous pharmaceutical composition comprising  
 5-[(2RS)-2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-ylmethyl]-  
 pyrimidine-2,4-diamine in form of the water soluble methanesulfonic acid  
 salt, a physiol. sodium chloride solution, ethanol and Povidone 12 PF, the  
 liquid having a pH of over and above 4.8, but not higher than 5.2, and  
 wherein the oxygen amount is controlled to be 0.8 ppm or less; which can be  
 sterilized by filtration and/or by heated treatment, stored for longer  
 time periods and which can be use for bolus injection or diluted for i.v.  
 infusion.

IT 192314-93-5D, Iclaprim, addition salt 474793-41-4  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (aqueous pharmaceutical formulation comprising  
 5-[(2RS)-2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-ylmethyl]-  
 pyrimidine-2,4-diamine methanesulfonic salt for bolus injection or i.v.  
 infusion)

RN 192314-93-5 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)



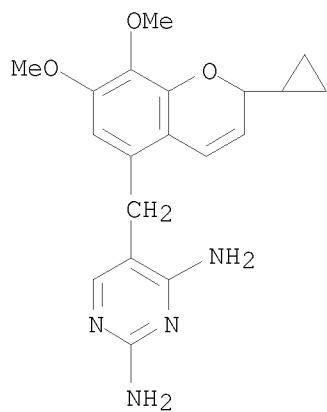
RN 474793-41-4 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 192314-93-5

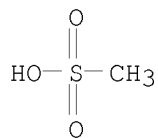
CMF C19 H22 N4 O3



CM 2

CRN 75-75-2

CMF C H4 O3 S

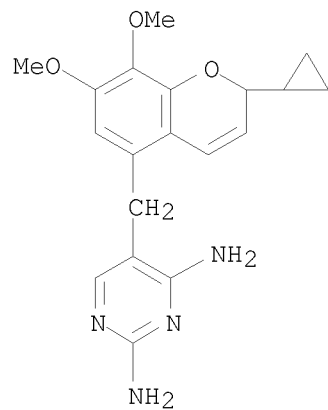


10/567,558

L4 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:1194632 CAPLUS  
 DN 151:418165  
 TI Gene expression profiling in the pulmonary artery in the selection of  
 therapies for vascular-related diseases  
 IN Mann, David Marshall  
 PA Vascular Biosciences, Inc., USA  
 SO PCT Int. Appl., 115pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

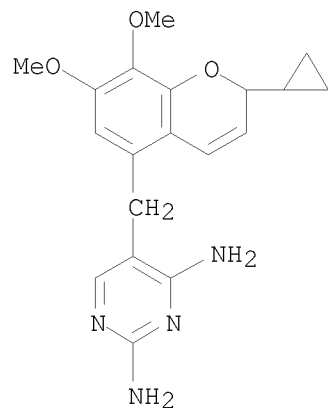
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009121031	A1	20091001	WO 2009-US38685	20090327
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
PRAI US 2008-40065P	P	20080327		
AB Methods of selecting treatment regimens for vascular-related diseases and disorders using gene expression profiles in affected blood vessels are described. Addnl., methods are disclosed involving diagnostic techniques to focus treatment regimens. Finally, methods of treating vascular-related disorder involving targeting microRNAs are also disclosed. Therapies suitable for treatment at different stages of the disease are identified.				
IT 192314-93-5, Iclaprim RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (in treatment of vascular disease; gene expression profiling in pulmonary artery in selection of therapies for vascular-related diseases)				
RN 192314-93-5 CAPLUS CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5- yl)methyl]- (CA INDEX NAME)				

10/567,558



L4 ANSWER 5 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:1139997 CAPLUS  
 DN 151:332024  
 TI Efficacy of iclaprim against wild-type and thymidine kinase-deficient methicillin-resistant *Staphylococcus aureus* isolates in an in vitro fibrin clot model  
 AU Entenza, Jose M.; Haldimann, Andreas; Giddey, Marlyse; Lociuro, Sergio; Hawser, Stephen; Moreillon, Philippe  
 CS Department of Fundamental Microbiology, University of Lausanne, Lausanne, 1015, Switz.  
 SO Antimicrobial Agents and Chemotherapy (2009), 53(9), 3635-3641  
 CODEN: AMACQ; ISSN: 0066-4804  
 PB American Society for Microbiology  
 DT Journal  
 LA English  
 AB Iclaprim is a novel diaminopyrimidine antibiotic that is active against methicillin-resistant *Staphylococcus aureus* (MRSA). However, it is known that the activity of diaminopyrimidines against *S. aureus* is antagonized by thymidine through uptake and conversion to thymidylate by thymidine kinase. Unlike with humans, for whom thymidine levels are low, thymidine levels in rodents are high, thus precluding the accurate evaluation of iclaprim efficacy in animal models. We have studied the bactericidal activity of iclaprim against an isogenic pair of MRSA isolates, the wild-type parent AW6 and its thymidine kinase-deficient mutant AH1252, in an in vitro fibrin clot model. Clots, which were aimed at mimicking vegetation structure, were made from human or rat plasma containing either the parent AW6 or the mutant AH1252, and they were exposed to homologous serum supplemented with iclaprim (3.5 µg/mL), trimethoprim-sulfamethoxazole (TMP-SMX; 8/40 µg/mL), vancomycin (40 µg/mL), or saline, each of which was added one time for 48 h. In rat clots, iclaprim and TMP-SMX were bacteriostatic against the parent, AW6. In contrast, they were bactericidal ( $\geq 3 \log_{10}$  CFU/clot killing of the original inoculum) against the mutant AH1252. Vancomycin was the most active drug against AW6 ( $P < 0.05$ ), but it showed an activity similar those of iclaprim and TMP-SMX against AH1252. In human clots, iclaprim was bactericidal against both AW6 and AH1252 strains and was as effective as TMP-SMX and vancomycin ( $P > 0.05$ ). Future studies of animals using simulated human kinetics of iclaprim and thymidine kinase-deficient MRSA, which eliminate the thymidine-induced confounding effect, are warranted to support the use of iclaprim in the treatment of severe MRSA infections in humans.  
 IT 192314-93-5, Iclaprim  
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (antibiotic activity of iclaprim against wild-type and thymidine kinase-deficient methicillin-resistant *Staphylococcus aureus*)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)

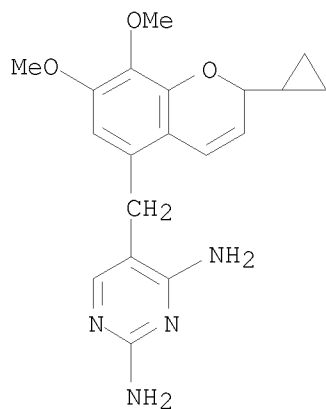
10/567,558



RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

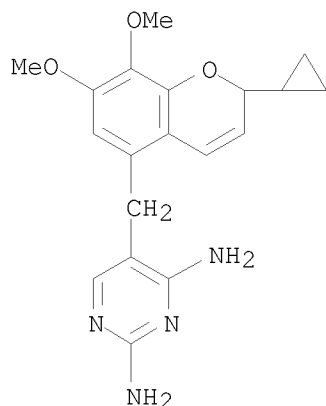


L4 ANSWER 6 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:902223 CAPLUS  
 DN 151:142941  
 TI Antimicrobial development in the era of emerging resistance  
 AU Sorlozano, Antonio; Carrasco, Cristina; Cabeza, Jose; Villegas, Enrique;  
 Gutierrez, Jose  
 CS Department of Microbiology, School of Medicine, University of Granada,  
 Spain  
 SO Mini-Reviews in Medicinal Chemistry (2009), 9(8), 938-955  
 CODEN: MMCIAE; ISSN: 1389-5575  
 PB Bentham Science Publishers Ltd.  
 DT Journal; General Review  
 LA English  
 AB A review. Antibiotics currently under study by the Food and Drugs  
 Administration include: faropenem (for treatment of sinusitis, bronchitis,  
 and community-acquired pneumonia), dalbavancin (for catheter infections),  
 telavancin (for treatment of nosocomial pneumonia),oritavancin (for  
 bacteremia), ceftobiprole and iclaprim (for pneumonias). Moreover, all of  
 them would be useful for skin and soft tissue infections.  
 IT 192314-93-5, Iclaprim  
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (antibiotic activity and resistance of faropenem, dalbavancin,  
 telavancin, ceftobiprole, and iclaprim against skin and soft tissue  
 infections)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)



RE.CNT 158 THERE ARE 158 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:892742 CAPLUS  
 DN 151:353789  
 TI Evidence based approach to the treatment of community-associated  
 methicillin-resistant *Staphylococcus aureus*  
 AU Peppard, William J.; Daniels, Anne; Fehrenbacher, Lynne; Winner, Jamie  
 CS Froedtert Hospital, Milwaukee, WI, USA  
 SO Infection and Drug Resistance (2009), 2, 27-40  
 CODEN: IDRNAV; ISSN: 1178-6973  
 URL: <http://www.dovepress.com/getfile.php?fileID=4936>  
 PB Dove Medical Press (NZ) Ltd.  
 DT Journal; General Review; (online computer file)  
 LA English  
 AB A review. Community-associated methicillin-resistant *Staphylococcus aureus*  
 (CA-MRSA) infections have increased dramatically over the last two  
 decades. The types of infections can range from complicated skin and skin  
 structure infections (cSSSI) to pneumonia and endocarditis. Oral  
 antimicrobial therapy, such as trimethoprim-sulfamethoxazole, clindamycin,  
 long-acting tetracyclines, or linezolid may provide enhanced benefit to  
 those with uncomplicated cutaneous lesions when used in conjunction with  
 incision and drainage in an outpatient setting. However, resistance,  
 susceptibilities, patient-specific circumstances, and adverse effects can  
 impact a healthcare professional's choice of antibiotics. In patients  
 with complicated infections requiring hospitalization or parenteral  
 treatment, vancomycin remains the drug of choice, even though increased  
 resistance and decreased efficacy have crept into clin. practice.  
 Linezolid, quinupristin/dalfopristin, daptomycin, and tigecycline are  
 alternative i.v. agents for the treatment of CA-MRSA. Investigational  
 agents such as dalbavancin, telavancin, oritavancin, iclaprim,  
 ceftobiprole, ceftaroline, and others may expand our therapeutic  
 armamentarium for the treatment of infections caused by CA-MRSA in the  
 future.  
 IT 192314-93-5, Iclaprim  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (evidence based approach to treatment of community-associated  
 methicillin-resistant *Staphylococcus* to patients discussed)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)

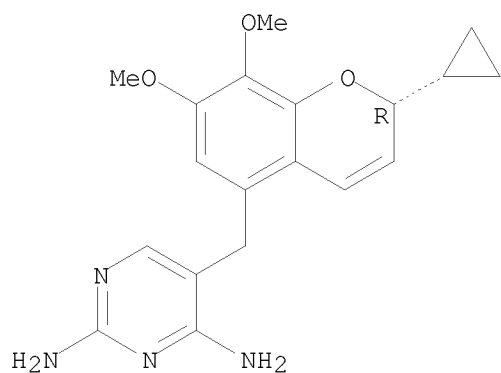


10/567,558

RE.CNT 91      THERE ARE 91 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:884378 CAPLUS  
 DN 152:254226  
 TI Inhibitory properties and X-ray crystallographic study of the binding of  
 AR-101, AR-102 and iclaprim in ternary complexes with NADPH and  
 dihydrofolate reductase from *Staphylococcus aureus*  
 AU Oefner, Christian; Parisi, Sandro; Schulz, Henk; Lociuero, Sergio; Dale,  
 Glenn E.  
 CS Arpida Ltd, Reinach, CH-4153, Switz.  
 SO Acta Crystallographica, Section D: Biological Crystallography (2009),  
 D65(8), 751-757  
 CODEN: ABCRE6; ISSN: 0907-4449  
 PB Wiley-Blackwell  
 DT Journal  
 LA English  
 AB Iclaprim is a novel dihydrofolate reductase (DHFR) inhibitor belonging to  
 the 2,4-diaminopyrimidine class of antibiotics, of which trimethoprim  
 (TMP) is the most well known representative. Iclaprim exhibits potent  
 bactericidal activity against major Gram-pos. pathogens, notably  
 methicillin-sensitive *Staphylococcus aureus* (MSSA) and  
 methicillin-resistant *S. aureus* (MRSA) phenotypes, including TMP-resistant  
 strains. The inhibition properties of racemic iclaprim and of the two  
 enantiomers, termed AR-101 and AR-102, towards *S. aureus* wild-type DHFR  
 and TMP-resistant F98Y mutant DHFR were determined and compared. Similar to  
 TMP, AR-101, AR-102 and iclaprim are all competitive inhibitors with  
 respect to the substrate dihydrofolate. Iclaprim, AR-101 and AR-102  
 demonstrated little or no difference in activity towards these enzymes and  
 were significantly more potent than TMP. The crystal structures of *S.*  
*aureus* DHFR and F98Y mutant DHFR were determined as ternary complexes with  
 NADPH and either AR-101, AR-102 or iclaprim. The binding modes of the  
 inhibitors were analyzed and compared. The X-ray crystallog. data explain  
 the binding modes of all mols. well and can be used to rationalize the  
 equipotent affinity of AR-101, AR-102 and iclaprim, which is also  
 reflected in their antibacterial properties.  
 IT 1208116-65-7 1208116-66-8  
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP  
 (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (iclaprim, AR-101 and AR-102 than trimethoprim were inhibitors that  
 were one order of magnitude more potent towards wild-type and mutant *S.*  
*aureus* DHFR as evident from X-ray crystallog. data determined as ternary  
 complexes with NADPH)  
 RN 1208116-65-7 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[[ (2R)-2-cyclopropyl-7,8-dimethoxy-2H-1-  
 benzopyran-5-yl]methyl]- (CA INDEX NAME)

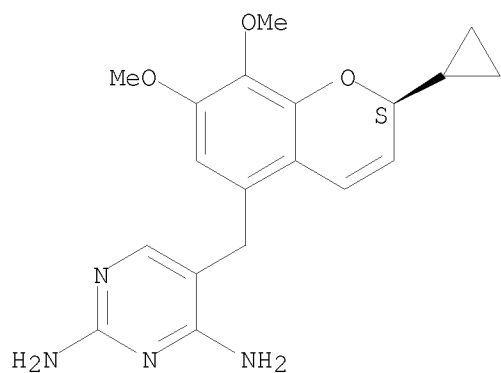
Absolute stereochemistry.



RN 1208116-66-8 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[[[(2S)-2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



IT 192314-93-5, Iclaprim

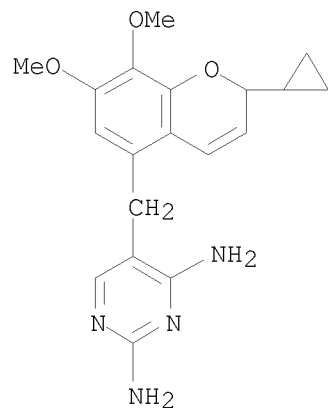
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(iclaprim, AR-101 and AR-102 than trimethoprim were inhibitors that were one order of magnitude more potent towards wild-type and mutant S. aureus DHFR as evident from X-ray crystallog. data determined as ternary complexes with NADPH)

RN 192314-93-5 CAPLUS

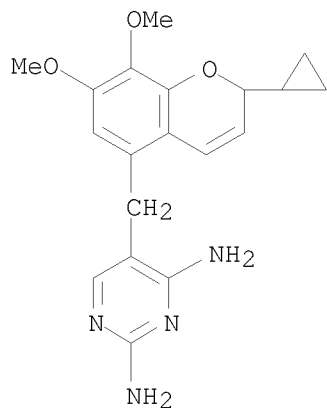
CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)

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RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

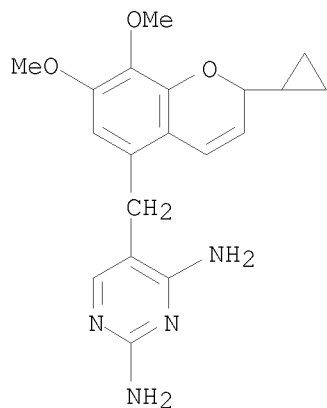
L4 ANSWER 9 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:831982 CAPLUS  
 DN 151:93359  
 TI Multicenter, randomized study of the efficacy and safety of intravenous  
 iclaprim in complicated skin and skin structure infections  
 AU Krievins, D.; Brandt, R.; Hawser, S.; Hadvary, P.; Islam, K.  
 CS Stradins Clinical University Hospital, Riga, Latvia  
 SO Antimicrobial Agents and Chemotherapy (2009), 53(7), 2834-2840  
 CODEN: AMACCQ; ISSN: 0066-4804  
 PB American Society for Microbiology  
 DT Journal  
 LA English  
 AB Iclaprim is a novel antibacterial agent that is currently in development  
 for the treatment of complicated skin and skin structure infections  
 (cSSSI). Iclaprim specifically and selectively inhibits bacterial  
 dihydrofolate reductase, a critical enzyme in the bacterial folate pathway,  
 and exhibits an extended spectrum of activity against various resistant  
 pathogens, including methicillin (methicillin)-resistant Staphylococcus  
 aureus (MRSA). The objective of this randomized, double-blind phase II  
 study was to compare the efficacy and safety of iclaprim to those of  
 vancomycin in patients with cSSSI. Patients were randomized to receive  
 0.8 mg iclaprim/kg of body weight, 1.6 mg/kg iclaprim, or 1 g vancomycin  
 twice a day for 10 days. Clin. cure rates for the 0.8- and  
 1.6-mg/kg-iclaprim treatment groups were comparable to that for the  
 vancomycin treatment group (26/28 patients [92.9%], 28/31 patients  
 [90.3%], and 26/28 patients [92.9%], resp.). Iclaprim also showed high  
 microbiol. eradication rates. Iclaprim exhibited an eradication rate of  
 80% and 72% vs. 59% observed with vancomycin for S. aureus, the pathogen most  
 frequently isolated at baseline. Five MRSA cases were observed, four in the  
 0.8-mg/kg-iclaprim arm and one in the vancomycin arm, and all were both  
 clin. and microbiol. cured. Iclaprim exhibited a safety profile similar  
 to that of vancomycin, an established drug for the treatment of cSSSI.  
 Results from this study indicate that iclaprim is a promising new therapy  
 for the treatment of cSSSI, in particular those caused by S. aureus,  
 including MRSA.  
 IT 192314-93-5, Iclaprim  
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (iclaprim against complicated skin and skin structure infections by  
 resistant Staphylococcus aureus and Streptococcus pyogenes)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)



OSC.G	1	THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
RE.CNT	26	THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
		ALL CITATIONS AVAILABLE IN THE RE FORMAT

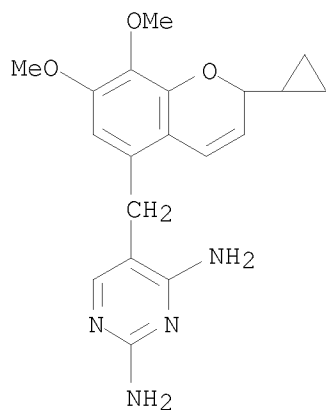


L4 ANSWER 10 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:829987 CAPLUS  
 DN 152:183011  
 TI Iclaprim, a novel diaminopyrimidine for the treatment of resistant  
 gram-positive infections  
 AU Sincak, Carrie A.; Schmidt, Justin M.  
 CS USA  
 SO Annals of Pharmacotherapy (2009), 43(6), 1107-1114  
 CODEN: APHRER; ISSN: 1060-0280  
 PB Harvey Whitney Books Co.  
 DT Journal; General Review  
 LA English  
 AB Objective: To review the pharmacol., microbiol., in vitro susceptibility,  
 pharmacokinetics, clin. trial data, safety, and tolerability of iclaprim,  
 a novel dihydrofolate reductase (DHFR) inhibitor. Data Sources: A MEDLINE  
 search was conducted from 1966 through Dec. 2008. Addnl. sources included  
 abstrs. from meetings of the Interscience Conference on Antimicrobial  
 Agents and Chemotherapy and the Infectious Diseases Society of America  
 from 2001 to 2008 and information available from the manufacturer's Web  
 Site. Study Selection And Data Extraction: In vitro and clin. studies, in  
 addition to Phase 1, 2, and 3 clin. trials, were included. Data Synthesis:  
 Iclaprim, a novel diaminopyrimidine and DHFR antagonist, has a mechanism  
 of action similar to that of trimethoprim. It has in vitro activity  
 mainly against gram-pos. organisms, including resistant Staphylococcus  
 aureus. In Phase 2 and 3 clin. trials, oral and i.v. administration of  
 iclaprim was effective and well tolerated for the treatment of complicated  
 skin and skin structure infections (cSSSI). Trials are currently ongoing  
 for the treatment of ventilator-associated and health-care-associated  
 pneumonia.  
 Conclusions: Iclaprim is a promising antimicrobial agent for the treatment  
 of gram-pos. organisms, including resistant S. aureus and trimethoprim-,  
 macrolide-, fluoroquinolone-, and glycopeptide-resistant strains. Addnl.,  
 in vitro activity similar to that of trimethoprim has been observed against  
 gram-neg. and atypical organisms.  
 IT 192314-93-5, Iclaprim  
 RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of  
 action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU  
 (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (iclaprim, novel diaminopyrimidine for treatment of resistant gram-pos.  
 infections)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)



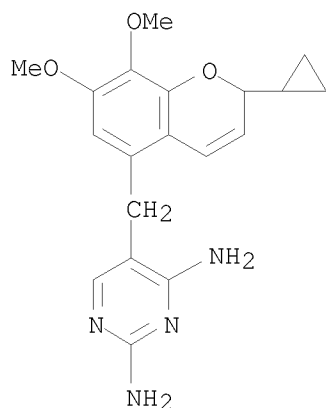
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RE.CNT	42	THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
		ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:585410 CAPLUS  
 DN 150:467424  
 TI Potency and bactericidal activity of iclaprim against recent clinical Gram-positive isolates  
 AU Sader, Helio S.; Fritsche, Thomas R.; Jones, Ronald N.  
 CS JMI Laboratories, North Liberty, IA, USA  
 SO Antimicrobial Agents and Chemotherapy (2009), 53(5), 2171-2175  
 CODEN: AMACCQ; ISSN: 0066-4804  
 PB American Society for Microbiology  
 DT Journal  
 LA English  
 AB The in vitro activity of iclaprim, a novel diaminopyrimidine derivative, was evaluated against 5,937 recent gram-pos. clin. isolates collected in the United States and Europe. Iclaprim demonstrated potent activity against *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]), beta-hemolytic *Streptococcus* spp., and *Enterococcus faecalis* strains tested. In addition, iclaprim exhibited bactericidal activity against all *S. aureus* strains tested, including MRSA.  
 IT 192314-93-5, Iclaprim  
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (antibiotic activity of iclaprim against gram-pos. pathogen)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



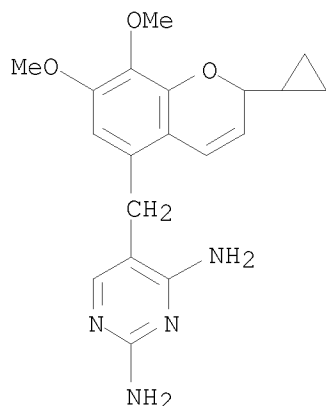
OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)  
 RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:525174 CAPLUS  
 DN 151:417301  
 TI Forthcoming therapeutic perspectives for infections due to  
 multidrug-resistant Gram-positive pathogens  
 AU Cornaglia, G.; Rossolini, G. M.  
 CS Dipartimento di Patologia, Sezione di Microbiologia, Università di Verona,  
 Verona, Italy  
 SO Clinical Microbiology and Infection (2009), 15(3), 218-223  
 CODEN: CMINFM; ISSN: 1198-743X  
 PB Wiley-Blackwell  
 DT Journal; General Review  
 LA English  
 AB A review. Multidrug resistance in Gram-pos. pathogens emerged as a major  
 therapeutic challenge over two decades ago. The worldwide spread of  
 methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-resistant  
 enterococci and other resistant Gram-pos. pathogens had a major impact on  
 antibiotic policies, and prompted the discovery and development of new  
 antibiotics to combat difficult-to-treat infections caused by such  
 pathogens. Several new antibiotics active against multidrug-resistant  
 Gram-pos. pathogens have recently been introduced into clin. practice, and  
 the antibiotic pipeline contains addnl. anti-Gram-pos. drugs at an  
 advanced stage of development, including new glycopeptides (dalbavancin,  
 oritavancin, and telavancin), new anti-MRSA  $\beta$ -lactams (ceftobiprole),  
 and new diaminopyrimidines (iclaprim). This article provides a brief  
 overview of these upcoming agents, partially based on the material  
 presented at the ESCMID Conference entitled 'Fighting infections due to  
 multidrug-resistant Gram-positives' and on the most recent literature.  
 IT 192314-93-5, Iclaprim  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (iclaprim may be effective in treatment of patient with infection due  
 to multidrug resistant *Staphylococcus aureus* or *Enterococcus*)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)



OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

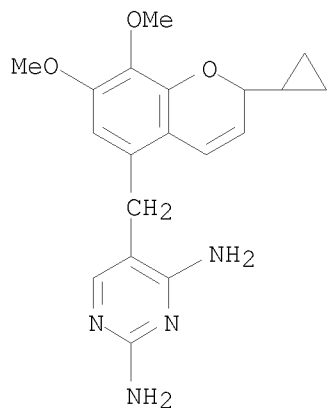
L4 ANSWER 13 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:451763 CAPLUS  
 DN 150:467408  
 TI In vitro activity of iclaprim against respiratory and bacteremic isolates of *Streptococcus pneumoniae*  
 AU Zhanel, George G.; Karlowsky, James A.  
 CS Department of Medical Microbiology and Infectious Diseases, Faculty of Medicine, University of Manitoba, Winnipeg, MB, Can.  
 SO Antimicrobial Agents and Chemotherapy (2009), 53(4), 1690-1692  
 CODEN: AMACCQ; ISSN: 0066-4804  
 PB American Society for Microbiology  
 DT Journal  
 LA English  
 AB Iclaprim, a novel dihydrofolate reductase inhibitor, inhibited 90% of the clin. isolates (MIC90) of *Streptococcus pneumoniae* (n = 785) collected by a national surveillance program at a concentration of 1 µg/mL. The MIC90 for iclaprim was 7 doubling dilns. lower for trimethoprim-sulfamethoxazole-susceptible isolates (n = 670; MIC90, 0.06 µg/mL) than for trimethoprim-sulfamethoxazole-resistant isolates (n = 115; MIC90, ≥8 µg/mL). The potential clin. utility of iclaprim to treat patients with pneumococcal infections may depend upon the current prevalence of resistance to trimethoprim-sulfamethoxazole in this pathogen.  
 IT 192314-93-5, Iclaprim  
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (in vitro activity of iclaprim against respiratory and bacteremic isolates of *Streptococcus pneumoniae*)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)  
 RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
AN 2009:325049 CAPLUS  
DN 150:510000  
TI Increased hydrophobic interactions of iclaprim with *Staphylococcus aureus* dihydrofolate reductase are responsible for the increase in affinity and antibacterial activity  
AU Oefner, Christian; Bandera, Monica; Haldimann, Andreas; Laue, Heike; Schulz, Henk; Mukhija, Seema; Parisi, Sandro; Weiss, Laurent; Lociuero, Sergio; Dale, Glenn E.  
CS Arpida AG, Reinach, CH-4153, Switz.  
SO Journal of Antimicrobial Chemotherapy (2009), 63(4), 687-698  
CODEN: JACHDX; ISSN: 0305-7453  
PB Oxford University Press  
DT Journal  
LA English  
AB Iclaprim is a novel 2,4-diaminopyrimidine that exhibits potent, rapid bactericidal activity against major Gram-pos. pathogens, including methicillin-susceptible *Staphylococcus aureus* and methicillin-resistant *S. aureus*, and is currently in clin. development for the treatment of complicated skin and skin structure infections. An understanding of the known mechanism of resistance to trimethoprim led to the design of this new inhibitor, with improved affinity towards dihydrofolate reductase (DHFR) from *S. aureus* and clin. useful activity against *S. aureus* including isolates resistant to trimethoprim. The objective of this study was to characterize the mode of action of iclaprim and its inhibitory properties against DHFR. The mode of action of iclaprim was assessed by enzymic anal., direct binding studies, macromol. synthesis profiles, synergy and antagonism studies to define its role as an inhibitor of DHFR. The binding properties of iclaprim to DHFR were compared with those of trimethoprim by X-ray crystallog. The enzymic properties, direct binding and X-ray crystallog. studies delineated the mode of interaction with DHFR and the reason for the increased affinity of iclaprim towards the enzyme. The effect of iclaprim on bacterial physiol. suggests that iclaprim behaves as a classical antibacterial DHFR inhibitor, as previously documented for trimethoprim. Iclaprim binds and inhibits bacterial DHFR in a similar manner to trimethoprim. However, the increased hydrophobic interactions between iclaprim and DHFR account for increased affinity and, unlike trimethoprim, enable iclaprim to inhibit even the resistant enzyme with nanomolar affinity, thus overcoming the mechanism of trimethoprim resistance. The increased antibacterial activity and lower propensity for resistance make iclaprim a clin. promising and useful inhibitor.  
IT 192314-93-5, Iclaprim  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(increased hydrophobic interactions of iclaprim with *Staphylococcus aureus* dihydrofolate reductase are responsible for increase in affinity and antibacterial activity)  
RN 192314-93-5 CAPLUS  
CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)

10/567,558



OSC.G	6	THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
RE.CNT	51	THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
		ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:292596 CAPLUS  
 DN 150:313939  
 TI Deuterium-enriched iclaprim for treating methicillin-resistant  
 Staphylococcus aureus and/or Staphylococcus aureus  
 IN Czarnik, Anthony W.  
 PA Protia, LLC, USA  
 SO U.S. Pat. Appl. Publ., 10pp.  
 CODEN: USXXCO  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 20090069357	A1	20090312	US 2008-196599	20080822
PRAI	US 2007-970982P	P	20070909		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS MARPAT 150:313939

AB The present application describes deuterium-enriched iclaprim, pharmaceutically acceptable salt forms thereof, and methods of treating using the same. A method is also provided for treating a disease selected from methicillin-resistant Staphylococcus aureus and/or Staphylococcus aureus, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the deuterium-enriched compds. of the present invention or a pharmaceutically acceptable salt thereof. Various deuterium-enriched iclaprim derivs. are suggested in the examples.

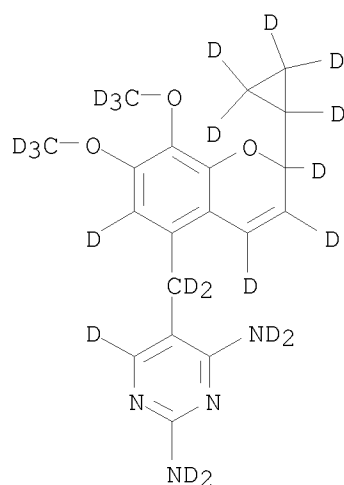
IT 1130072-51-3 1130072-52-4 1130072-54-6  
 1130072-55-7 1130072-56-8 1130072-57-9  
 1130072-58-0 1130072-59-1

RL: PRPH (Prophetic); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(deuterium-enriched iclaprim for treating methicillin-resistant Staphylococcus aureus or Staphylococcus aureus)

RN 1130072-51-3 CAPLUS

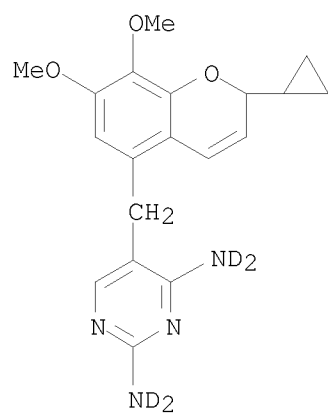
CN INDEX NAME NOT YET ASSIGNED



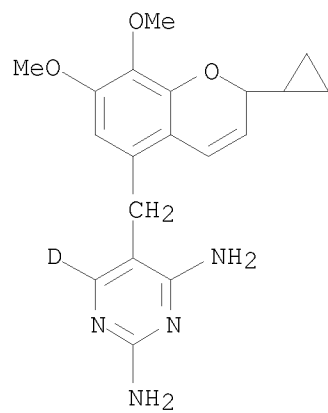


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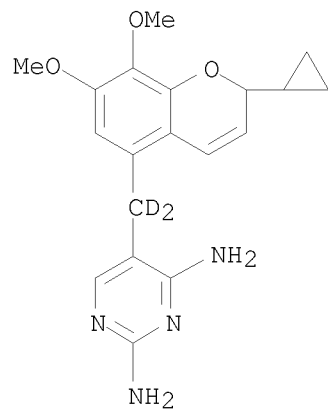
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CN INDEX NAME NOT YET ASSIGNED



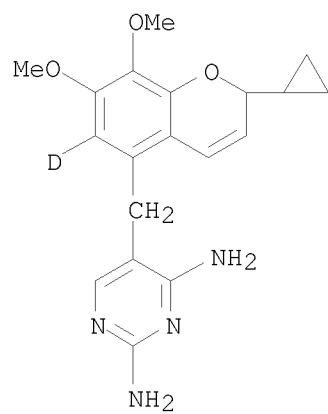
RN 1130072-54-6 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED



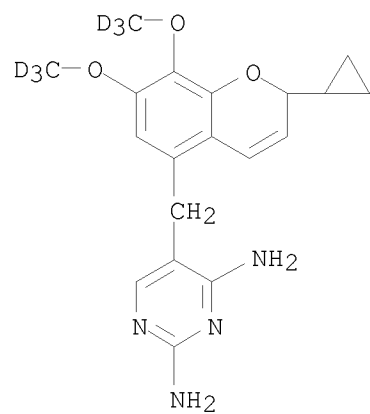
RN 1130072-55-7 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED



RN 1130072-56-8 CAPLUS  
 CN INDEX NAME NOT YET ASSIGNED

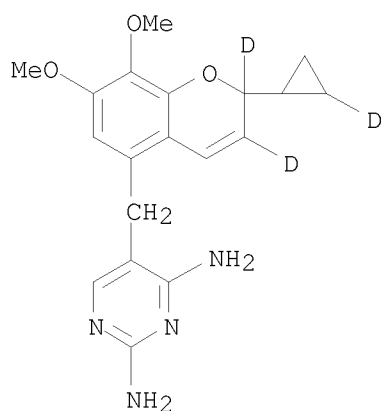


RN 1130072-57-9 CAPLUS  
 CN INDEX NAME NOT YET ASSIGNED

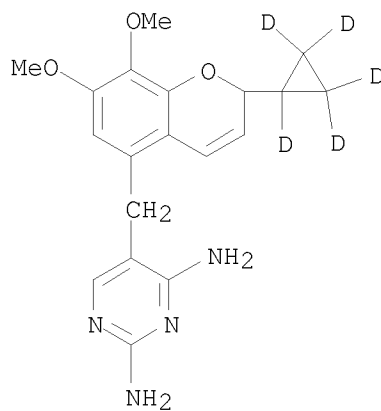


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RN 1130072-58-0 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

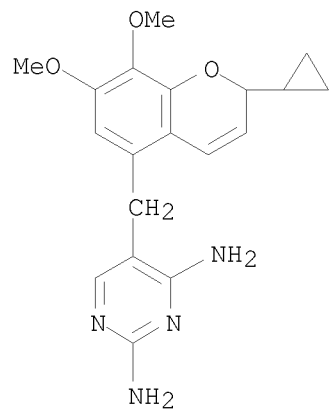


RN 1130072-59-1 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

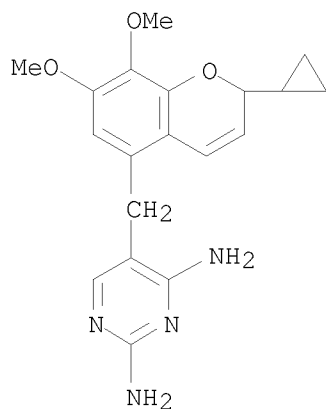


IT 192314-93-5D, Iclaprim, deuterium-enriched  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(deuterium-enriched iclaprim for treating methicillin-resistant  
Staphylococcus aureus or Staphylococcus aureus)  
RN 192314-93-5 CAPLUS  
CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)

10/567,558

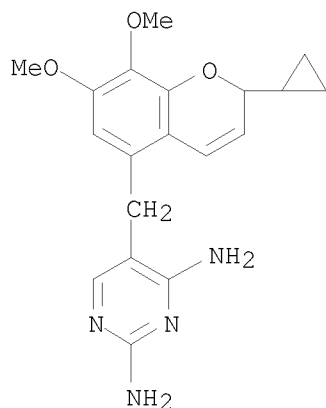


L4 ANSWER 16 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:271854 CAPLUS  
 DN 151:259385  
 TI Iclaprim: a novel dihydrofolate reductase inhibitor for skin and soft tissue infections  
 AU Morgan, Andrew; Cofer, Christine; Stevens, Dennis L.  
 CS Veterans Affairs Medical Center, Boise, ID, USA  
 SO Future Microbiology (2009), 4(2), 131-144  
 CODEN: FMUIAR; ISSN: 1746-0913  
 PB Future Medicine Ltd.  
 DT Journal; General Review  
 LA English  
 AB A review. Antibiotic resistance is an ever-increasing concern in the treatment of severe skin and skin-structure infections, pneumonia, bacteremia and other serious infections caused by methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *S. aureus*, group A *Streptococcus* and vancomycin-resistant *Enterococcus*. In this review, we summarize the current status of both US FDA-approved and investigational agents aimed at this group of pathogens. We also describe, in detail, the chemical, mechanism of action, pharmacokinetic properties and spectrum of microbiol. activity of iclaprim, a novel dihydrofolate reductase inhibitor recently awarded fast-track approval status by the FDA. Finally, we review the clin. efficacy of iclaprim compared with linezolid for skin and skin-structure infections as demonstrated in Phase III randomized, controlled trials, and comment on its potential role in the treatment of other severe infections with drug-resistant Gram-pos. pathogens.  
 IT 192314-93-5, Iclaprim  
 RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (iclaprim was effective in patient with skin and soft tissue infections caused by antibiotic-resistant Gram-pos. organism)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

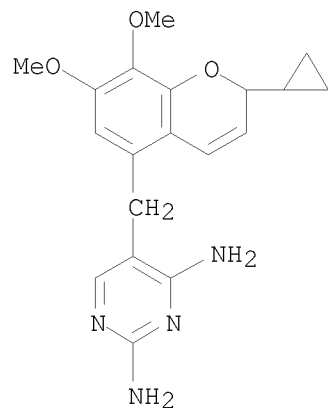
L4 ANSWER 17 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:226464 CAPLUS  
 DN 150:255406  
 TI Activity of iclaprim against clinical isolates of *Streptococcus pyogenes*  
 and *Streptococcus agalactiae*  
 AU Morrissey, I.; Maher, K.; Hawser, S.  
 CS Microbiology, Quotient Bioresearch Ltd, Fordham, CB7 5WW, UK  
 SO Journal of Antimicrobial Chemotherapy (2009), 63(2), 413-414  
 CODEN: JACHDX; ISSN: 0305-7453  
 PB Oxford University Press  
 DT Journal  
 LA English  
 AB The in vitro activities of iclaprim, trimethoprim/sulfamethoxazole  
 (co-trimoxazole), clarithromycin, clindamycin, linezolid, penicillin G,  
 levofloxacin, and vancomycin against clin. isolates of *Streptococcus*  
*pyogenes* and *S. agalactiae* were investigated. Iclaprim was more active  
 against *S. pyogenes* than co-trimoxazole, levofloxacin, linezolid, and  
 vancomycin. Activity against *S. agalactiae* was higher than those of  
 levofloxacin, linezolid, clarithromycin, and clindamycin and comparable to  
 those of co-trimoxazole, penicillin, and vancomycin. Iclaprim was active  
 against macrolide-resistant isolates of *S. pyogenes* and *agalactiae*.  
 IT 192314-93-5, Iclaprim  
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (antibiotic activity of iclaprim against *Streptococcus pyogenes* and  
*Streptococcus agalactiae*)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)



OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)  
 RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:201306 CAPLUS  
 DN 151:115267  
 TI What's new and not so new on the antimicrobial horizon?  
 AU French, G. L.  
 CS Department of Infection, King's College and Guy's and St Thomas Hospital,  
 London, UK  
 SO Clinical Microbiology and Infection (2008), 14(Suppl. 6), 19-29  
 CODEN: CMINFM; ISSN: 1198-743X  
 PB Wiley-Blackwell  
 DT Journal; General Review  
 LA English  
 AB A review. Despite increasing antimicrobial resistance and multiple drug  
 resistance in clin. isolates of both Gram-pos. and Gram-neg. bacteria,  
 there are few novel antimicrobial agents in development. The few new  
 agents that have been recently licensed have tended to have narrow spectra  
 of activity, focused on Gram-pos. pathogens, especially methicillin-resistant  
 Staphylococcus aureus (MRSA). This situation is rightly causing concern  
 among clinicians and public health authorities worldwide. This article  
 reviews available data on three new antibacterials currently in  
 development. The cephalosporin ceftobiprole is active against MRSA,  
 Enterococcus faecalis and penicillin-resistant Streptococcus pneumoniae,  
 but otherwise has a spectrum of activity similar to that of other recent  
 cephalosporins. In a clin. trial, ceftobiprole was non-inferior to  
 vancomycin for the treatment of MRSA-associated complicated skin and skin  
 structure infections (cSSSIs). Doripenem, a new carbapenem, has some  
 activity against MRSA, but otherwise has an anti-Gram-pos. spectrum of  
 activity similar to that of imipenem and an anti-Gram-neg. spectrum  
 similar to that of meropenem. In a clin. trial, it was non-inferior to  
 meropenem for the treatment of complicated intra-abdominal infections.  
 Iclaprim is a dihydrofolate reductase inhibitor with greatly enhanced  
 activity, as compared with trimethoprim, against a range of Gram-pos. and  
 Gram-neg. pathogens. The limited literature concerning this agent has  
 concentrated on its potential role in the treatment of infections with  
 Gram-pos. bacteria. A clin. trial has demonstrated the non-inferiority of iclaprim,  
 as compared with linezolid, in the treatment of cSSSIs, including those  
 associated with MRSA.  
 IT 192314-93-5, Iclaprim  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (new antibacterial agent iclaprim was useful in treatment of patient  
 with methicillin-resistant Staphylococcus aureus-associated complicated  
 skin and skin structure infection)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)

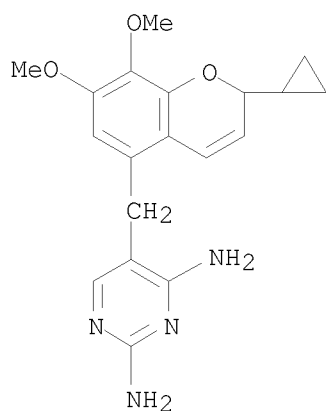
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RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

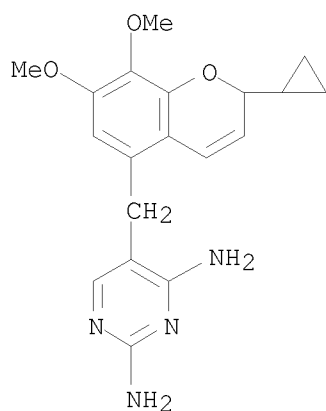


L4 ANSWER 19 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:199769 CAPLUS  
 DN 151:331950  
 TI In vitro activity of iclaprim and comparison agents tested against  
 Neisseria gonorrhoeae including medium growth supplement effects  
 AU Jones, Ronald N.; Biedenbach, Douglas J.; Sader, Helio S.  
 CS JMI Laboratories, North Liberty, IA, 512317, USA  
 SO Diagnostic Microbiology and Infectious Disease (2009), 63(3), 339-341  
 CODEN: DMIDDZ; ISSN: 0732-8893  
 PB Elsevier Inc.  
 DT Journal  
 LA English  
 AB Iclaprim is a novel diaminopyrimidine currently in phase III clin.  
 development. This study was conducted to determine the activity of iclaprim  
 compared with trimethoprim and other commonly prescribed drug classes  
 against a comprehensive collection of 156 Neisseria gonorrhoeae, including  
 subsets of organisms resistant to  $\beta$ -lactams and fluoroquinolones  
 (>60%). Iclaprim (MIC<sub>50/90</sub>, 4/8  $\mu$ g/mL) was 16-fold more potent than  
 trimethoprim (MIC<sub>50/90</sub>, 64/>64  $\mu$ g/mL), and medium growth supplements  
 did not adversely influence activity. Lack of cross-resistances for  
 iclaprim with other commonly used therapies could make iclaprim an  
 alternative for several sexually transmitted diseases (gonococci,  
 Chlamydia trachomatis).  
 IT 192314-93-5, Iclaprim  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (N. gonorrhoeae including organism resistant to  $\beta$ -lactams,  
 fluoroquinolones treated by iclaprim, trimethoprim, diverse drug show  
 iclaprim more potent, medium growth supplements not badly influence  
 activity, no cross-resistances with drugs)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)



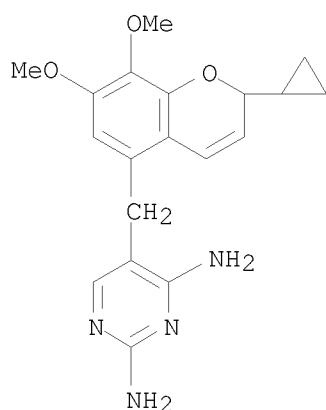
RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2008:1504105 CAPLUS  
 DN 151:94  
 TI Current and novel antibiotics against resistant Gram-positive bacteria  
 AU Perez, Federico; Salata, Robert A.; Bonomo, Robert A.  
 CS Division of Infectious Diseases and HIV Medicine, University Hospitals  
 Case Medical Center, Cleveland, OH, USA  
 SO Infection and Drug Resistance (2008), 1, 27-44  
 CODEN: IDRNAV; ISSN: 1178-6973  
 URL: [http://www.dovepress.com/articles.php?article\\_id=2207](http://www.dovepress.com/articles.php?article_id=2207)  
 PB Dove Medical Press (NZ) Ltd.  
 DT Journal; General Review; (online computer file)  
 LA English  
 AB A review. The challenge posed by resistance among Gram-pos. bacteria, epitomized by methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and vancomycin-intermediate and -resistant *S. aureus* (VISA and VRSA) is being met by a new generation of antimicrobials. This review focuses on the new  $\beta$ -lactams with activity against MRSA (ceftobiprole and ceftaroline) and on the new glycopeptides (oritavancin, dalbavancin, and telavancin). It will also consider the role of vancomycin in an era of existing alternatives such as linezolid, daptomycin and tigecycline. Finally, compds. in early development are described, such as iclaprim, friulimicin, and retapamulin, among others.  
 IT 192314-93-5, Iclaprim  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (iclaprim may be useful in patient with resistant Gram-pos. bacteria infection)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)  
 RE.CNT 150 THERE ARE 150 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 21 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
AN 2008:594822 CAPLUS  
DN 149:298726  
TI Physicochemical properties of antibacterial compounds: implications for drug discovery  
AU O'Shea, Rosemarie; Moser, Heinz E.  
CS Achaogen Pharmaceuticals Inc., South San Francisco, CA, 94080, USA  
SO Journal of Medicinal Chemistry (2008), 51(10), 2871-2878  
CODEN: JMCMAR; ISSN: 0022-2625  
PB American Chemical Society  
DT Journal  
LA English  
AB With the rise of multidrug-resistant pathogens and the need for novel antibiotics, it is critical to understand as much as possible from prior efforts and to apply learned lessons to the discovery of future antibiotics. One important parameter in particular has previously been mentioned but, in the view, not sufficiently analyzed: the physicochem. property space of antibacterial drugs. The authors selected 147 antibacterially active compds. that encompass both currently used drugs and compds. that are still under clin. investigation (see Methods for details). Where available, other property values were extracted from the literature, including protein binding and oral bioavailability in humans. This anal. suggests that natural products should be increasingly investigated again to identify novel antibacterial hits. Besides their high level of structural diversity, they are likely to better cover the required physicochem. property space for antibacterial compds. compared to synthetic mols. because of an increased d. of polar functionalities.  
IT 192314-93-5, Iclaprim  
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (physicochem. properties of antibacterial compds. and implications for drug discovery)  
RN 192314-93-5 CAPLUS  
CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)

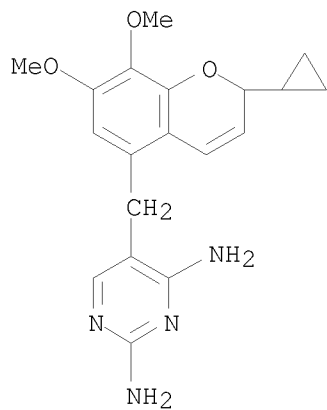


OSC.G 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)  
RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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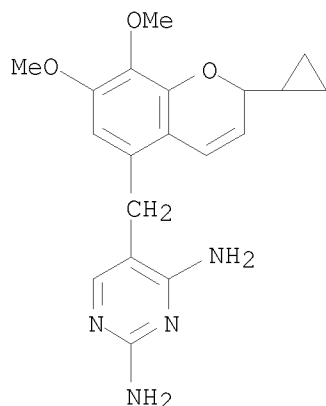
L4 ANSWER 22 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2008:477514 CAPLUS  
 DN 148:417108  
 TI Coagulase-negative staphylococcus infections - antibacterial therapy,  
 therapeutic problems, and novel antibacterial agents  
 AU Stock, Ingo  
 CS Bruehl bei Koeln, D-50321, Germany  
 SO Chemotherapie Journal (2008) 17(1), 10-24  
 CODEN: CHJOFT; ISSN: 0940-6735  
 PB Wissenschaftliche Verlagsgesellschaft mbH  
 DT Journal; General Review  
 LA German  
 AB A review. Several coagulase-neg. staphylococcus species are frequent  
 agents of a variety of nosocomial and community-acquired infections, in  
 particular in young children, infants, and in the elderly population.  
 They are the leading agents of nosocomial sepsis in neonates and frequent  
 causes of other blood-stream infections. Endocarditis and meningitis as  
 well as various infections of the urinary tract, soft tissue, wound, eye,  
 and skin are also attributed to these bacteria. The most frequent  
 pathogen of many of these infections is Staphylococcus epidermidis,  
 followed by S. hominis, S. haemolyticus, S. warneri, S. lugdunensis, and  
 S. saprophyticus. Problems concerning the antibacterial treatment of  
 staphylococcus infections arise from strains that have acquired  
 resistances to several agents of different antimicrobial sub-groups, i.e.,  
 beta-lactams, aminoglycosides, fluoroquinolones, macrolides, lincosamides,  
 fusidic acid, co-trimoxazole, and other antistaphylococcal agents.  
 Another problem are biofilms that are frequently generated by the bacteria  
 during indwelling medical device associated infections. Bacteria found in  
 biofilms are often poorly controlled by current antistaphylococcal agents.  
 Therefore, novel antibacterial substances with an enhanced activity  
 against multiresistant strains as well as biofilm forming bacteria are  
 strongly required. The currently most promising candidates for the  
 treatment of infections due to coagulase-neg. staphylococci comprise  
 linezolid, tigecycline and ceftobiprole as well as some new glycopeptides,  
 i.e., dalbavancin, oritavancin, and telavancin. Iclaprim, the topical  
 pleuromutilin retapamulin, the quinolone derivate DX-619 and the peptide  
 deformylase inhibitor LBM415 might also represent attractive therapeutic  
 agents and should be considered for further investigation.  
 IT 192314-93-5, Iclaprim  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (antibacterial therapy, therapeutic problems, and novel antibacterial  
 agents for coagulase-neg. staphylococcus infections)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)

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RE.CNT 130 THERE ARE 130 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2008:363860 CAPLUS  
 DN 150:486601  
 TI Iclaprim, a diaminopyrimidine dihydrofolate reductase inhibitor for the potential treatment of antibiotic-resistant staphylococcal infections  
 AU Peppard, William J.; Schuenke, Christopher D.  
 CS Froedtert Hospital, Milwaukee, WI, 53226, USA  
 SO Current Opinion in Investigational Drugs (Thomson Scientific) (2008), 9(2), 210-225  
 CODEN: COIDAZ; ISSN: 1472-4472  
 PB Thomson Scientific  
 DT Journal; General Review  
 LA English  
 AB A review. Arpida Ltd, under license from Roche AG, is developing the diaminopyrimidine dihydrofolate reductase inhibitor iclaprim for the potential treatment of methicillin-resistant *Staphylococcus aureus* infections, including complicated skin and skin structure infections and hospital-acquired pneumonia. Phase III cSSSI clin. trials have been completed and an NDA filing process is ongoing. A phase II clin. trial for hospital-acquired pneumonia is ongoing.  
 IT 192314-93-5, Iclaprim  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (diaminopyrimidine dihydrofolate reductase inhibitor iclaprim may be effective in treatment of patient with methicillin-resistant *Staphylococcus aureus* including complicated skin and skin structure infection and hospital-acquired pneumonia)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



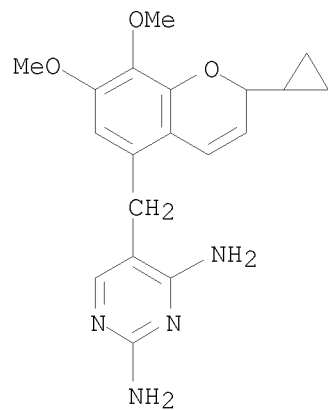
OSC.G 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)  
 RE.CNT 140 THERE ARE 140 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2008:223548 CAPLUS  
 DN 148:269428  
 TI Once-a-day antibiotic formulations for treatment of methicillin-resistant  
 Staphylococcus aureus infection  
 IN Flanner, Henry H.; Treacy, Donald; Tolle-Sander, Sanna; Burnside, Beth A.;  
 Rudnic, Edward  
 PA Middlebrook Pharmaceuticals, Inc., USA  
 SO PCT Int. Appl., 58pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

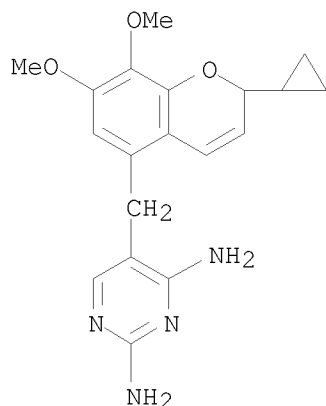
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2008021089	A2	20080221	WO 2007-US17552	20070807
	WO 2008021089	A3	20080821		
	W:	AE, AG, AL, AM, AN, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
	RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
	US 20100016333	A1	20100121	US 2007-890747	20070807
PRAI	US 2006-836026P	P	20060807		
	US 2006-836313P	P	20060808		
AB	Once-a-day oral antibiotic products for treating methicillin-resistant Staphylococcus aureus (MRSA) are provided, comprising a combination of at least 3 different antibiotics selected from RNA polymerase inhibiting antibiotics, phenazine antibiotics, dihydropteroate synthase inhibiting antibiotics, and dihydrofolate reductase inhibiting antibiotics, optionally in combination with a resistance inhibitor, preferably a LexA protease cleavage inhibitor. The product further comprises at least one component(s) selected from the group comprising immediate release components and modified release components, each component comprising a pharmaceutically acceptable carrier and at least one antibiotic. Thus, tablet cores were prepared containing rifapentin 65%, microcryst. cellulose 20%, polyvinylpyrrolidone (K30) 10%, and croscarmellose sodium 5%. Cores 75% were then film coated with 20% Et cellulose and 5% hydroxypropyl cellulose to obtain a one-a-day tablet formulation.				
IT	192314-93-5, Iclaprim RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (controlled-release antibiotic formulations for treatment of methicillin-resistant Staphylococcus aureus infection)				
RN	192314-93-5 CAPLUS				
CN	2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)				



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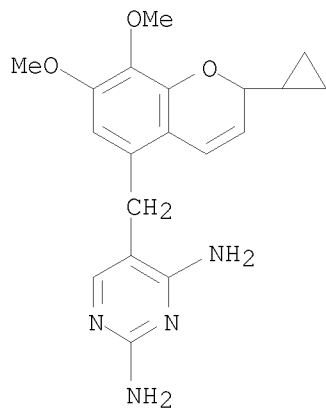
L4 ANSWER 25 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2007:1365617 CAPLUS  
 DN 148:116663  
 TI Effect of human plasma on the antimicrobial activity of iclaprim in vitro  
 AU Laue, H.; Valensise, T.; Seguin, A.; Hawser, S.; Lociuero, S.; Islam, K.  
 CS Arpida AG, Duggingerstrasse 23, Reinach, 4153, Switz.  
 SO Journal of Antimicrobial Chemotherapy (2007), 60(6), 1388-1390  
 CODEN: JACHDX; ISSN: 0305-7453  
 PB Oxford University Press  
 DT Journal  
 LA English  
 AB Iclaprim is a novel diaminopyrimidine for which a human plasma binding level of approx. 93% has been reported. The purpose of this study was to evaluate the effect of human plasma on the in vitro activity of iclaprim and to compare it with that of fusidic acid, teicoplanin and vancomycin, antibiotics with protein binding to human plasma of 97 %, >90 % and 55 %, resp. MICs were determined using 40 methicillin-susceptible *Staphylococcus aureus* (MSSA) and 38 methicillin-resistant *S. aureus* (MRSA) isolates in Mueller-Hinton broth (MHB) alone or in the presence of 50 % human plasma. MICs of iclaprim were not affected by the addition of human plasma. MIC ranges (MIC90) for iclaprim against MSSA and MRSA were <0.016-0.06 mg/L (MIC90 0.06 mg/L) and <0.016-0.5 mg/L (MIC90 0.06 mg/L), resp., in MHB and <0.016-0.125 mg/L (MIC90 0.06 mg/L) and <0.016-0.25 mg/L (MIC90 0.125 mg/L), resp., in the presence of human plasma. As expected, the antimicrobial activity of fusidic acid was greatly affected by the presence of human plasma (MIC elevations of 4- to >128-fold), whereas MICs of vancomycin remained unchanged. By contrast, despite the high protein binding, MICs of teicoplanin were only marginally affected by the presence of plasma with an MIC elevation of maximum 8-fold for two strains. This study demonstrates that human plasma does not affect the MIC of iclaprim in vitro.  
 IT 192314-93-5, Iclaprim  
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (effect of human plasma on antimicrobial activity of iclaprim in vitro in comparison with other antibiotics)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



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OSC.G	6	THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
RE.CNT	10	THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
		ALL CITATIONS AVAILABLE IN THE RE FORMAT

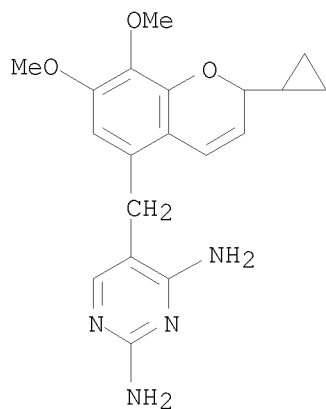
L4 ANSWER 26 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2007:1365584 CAPLUS  
 DN 148:49561  
 TI In vitro activity of the novel diaminopyrimidine, iclaprim, in combination with folate inhibitors and other antimicrobials with different mechanisms of action  
 AU Laue, H.; Weiss, L.; Bernardi, A.; Hawser, S.; Lociuero, S.; Islam, K.  
 CS Arpida AG, Reinach, 4153, Switz.  
 SO Journal of Antimicrobial Chemotherapy (2007), 50(6), 1391-1394  
 CODEN: JACHDX; ISSN: 0305-7453  
 PB Oxford University Press  
 DT Journal  
 LA English  
 AB To assess the synergistic potential of the novel diaminopyrimidine iclaprim (formerly AR-100, Ro 48-2622), a specific and selective inhibitor of microbial dihydrofolate reductase (DHFR), in combination with other antimicrobial agents with distinctly different mechanisms of action. In checkerboard studies, iclaprim was tested in combination with 32 different antimicrobial agents against Gram-pos., Gram-neg. and anaerobic bacteria including reference strains. Iclaprim was highly synergistic against the strains tested with the 2 sulfonamides selected, namely, sulfamethoxazole and sulfadiazine. With the other 28 antimicrobial agents, neither synergy nor antagonism was observed with macrolides, lincosamides, aminoglycosides, quinolones,  $\beta$ -lactams, trimethoprim, tetracyclines and glycopeptides. Furthermore, iclaprim exhibited no synergy or antagonism when evaluated in combination with metronidazole or aztreonam against a panel of 19 bacterial strains, including Gram-pos., Gram-neg. and selected anaerobic bacteria. In agreement with the mechanism of action of microbial DHFR inhibitors, iclaprim exhibited synergism with sulfonamides and exhibited neither antagonism nor synergy with all the other antibiotics tested. Notably, iclaprim exhibited indifference in combination with aztreonam and metronidazole against Gram-negatives and anaerobes, resp.  
 IT 192314-93-5, Iclaprim  
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (iclaprim antibiotic activity combined with dihydrofolate reductase inhibitors and other antibiotics)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



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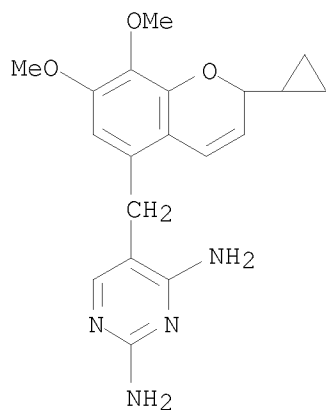
OSC.G	13	THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)
RE.CNT	10	THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
		ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 27 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2007:1286714 CAPLUS  
 DN 148:416885  
 TI Late stage antibacterial drugs in the clinical pipeline  
 AU Projan, Steven J.; Bradford, Patricia A.  
 CS Wyeth Research, Cambridge, MA, 02140, USA  
 SO Current Opinion in Microbiology (2007), 10(5), 441-446  
 CODEN: COMIF7; ISSN: 1369-5274  
 PB Elsevier B.V.  
 DT Journal; General Review  
 LA English  
 AB A review. Bacterial resistance to antimicrobial agents is a growing problem worldwide. Not only is issue compounded by the fact that there are fewer pharmaceutical companies conducting research to discover novel antimicrobials than in the past but development time lines have stretched so that a dozen years from discovery to the market is now the standard Eleven antibacterial drugs in late stage clin. development are discussed. Whereas many of these may successfully deal with resistant strains of Gram-pos. pathogens, there is very little in development to address the growing unmet medical need of multi-drug resistant Gram-neg. infections.  
 IT 192314-93-5, Iclaprim  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (iclaprim showed antibacterial activity against methicillin-resistant Staphylococcus aureus in patient)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



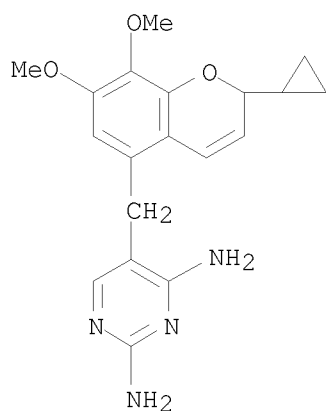
OSC.G 23 THERE ARE 23 CAPLUS RECORDS THAT CITE THIS RECORD (23 CITINGS)  
 RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 28 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2007:1283786 CAPLUS  
 DN 148:4860  
 TI Activity of iclaprim against Legionella pneumophila  
 AU Morrissey, Ian; Hawser, Stephen  
 CS GR Micro Ltd, London, NW1 3ER, UK  
 SO Journal of Antimicrobial Chemotherapy (2007), 60(4), 905-906  
 CODEN: JACHDX; ISSN: 0305-7453  
 PB Oxford University Press  
 DT Journal  
 LA English  
 AB Iclaprim is a new hydrofolate reductase inhibitor. This antibiotic can be used in combination with sulfonamides against Legionella pneumophila. Iclaprim was very active with 16-fold lower MIC50 or MIC90 than trimethoprim alone. Sulfamthoxazole was inactive and trimethoprim/sulfamethoxazole was also less active than iclaprim. Iclaprim was active similar to clarithromycin, but was less active than levofloxacin.  
 IT 192314-93-5, Iclaprim  
 RL: BSU (Biological study, unclassified); DMA (Drug mechanism of action); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (antibiotic activity of iclaprim against Legionella pneumophila)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



OSC.G 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)  
 RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

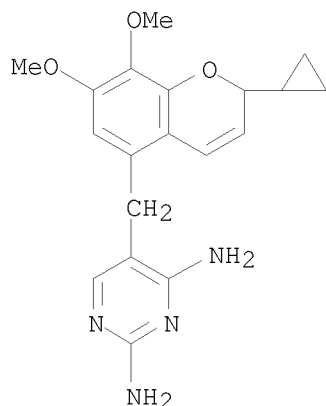
L4 ANSWER 29 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2007:1122440 CAPLUS  
 DN 148:102  
 TI Alternatives to vancomycin for the treatment of methicillin-resistant  
 Staphylococcus aureus infections  
 AU Micek, Scott T.  
 CS Department of Pharmacy, Barnes-Jewish Hospital, St. Louis, MO, USA  
 SO Clinical Infectious Diseases (2007), 45(Suppl. 3), S184-S190  
 CODEN: CIDIEL; ISSN: 1058-4838  
 PB University of Chicago Press  
 DT Journal; General Review  
 LA English  
 AB A review. Vancomycin remains the reference standard for the treatment of  
 systemic  
 infection caused by methicillin-resistant Staphylococcus aureus (MRSA).  
 However, as a result of limited tissue distribution, as well as the  
 emergence of isolates with reduced susceptibility and in vitro resistance  
 to vancomycin, the need for alternative therapies that target MRSA has  
 become apparent. New treatment options for invasive MRSA infections  
 include linezolid, daptomycin, tigecycline, and quinupristin/dalfopristin.  
 Addnl., a number of new anti-MRSA compds. are in development, including novel  
 glycopeptides (dalbavancin, telavancin, and oritavancin), ceftobiprole,  
 and iclaprim. The present article will review clin. issues surrounding  
 the newly marketed and investigational agents with activity against MRSA.  
 IT 192314-93-5, Iclaprim  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (iclaprim was used as alternative to vancomycin for treatment of  
 patient with methicillin-resistant Staphylococcus aureus infection)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)



OSC.G 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)  
 RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT



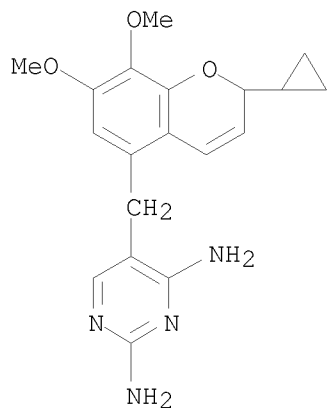
L4 ANSWER 30 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2007:930862 CAPLUS  
 DN 147:356140  
 TI Iclaprim  
 AU Kohlhoff, Stephan A.; Sharma, Roopali  
 CS Division of Pediatric Infectious Diseases, Department of Pediatrics, State  
 University of New York Downstate Medical Center, Brooklyn, NY, 11203, USA  
 SO Expert Opinion on Investigational Drugs (2007), 16(9), 1441-1448  
 CODEN: EOIDER; ISSN: 1354-3784  
 PB Informa Healthcare  
 DT Journal; General Review  
 LA English  
 AB A review. Iclaprim is a novel diaminopyrimidine, and an inhibitor of dihydrofolate reductase, which has shown potent, extended-spectrum in vitro activity against Gram-pos. bacteria, including methicillin-resistant *Staphylococcus aureus*, vancomycin-intermediate and vancomycin-resistant *S. aureus* and macrolide-, quinolone- and trimethoprim-resistant strains. In addition, iclaprim has demonstrated activity against *Streptococcus pneumoniae* including penicillin-, erythromycin-, levofloxacin- and trimethoprim/sulfamethoxazole-resistant strains. Furthermore, in vitro activity has also been observed against Gram-neg. bacteria and atypical bacteria. The pharmacokinetic profile of this agent reveals that iclaprim is available for i.v. and oral use, with good oral bioavailability. Phase II clin. trials have shown promise in its use for complicated skin and skin structure infections that are caused by methicillin-resistant *S. aureus* and two Phase III clin. trials have been recently completed for the same indication. Phase II trials evaluating the efficacy in respiratory infections are expected to start in 2007. At this early point in clin. development, the available reported data indicate potential for iclaprim as a new antibiotic for parenteral and oral treatment of complicated skin and skin structure infections.  
 IT 192314-93-5, Iclaprim  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (antibacterial action of iclaprim against antibiotic resistant bacteria)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



10/567,558

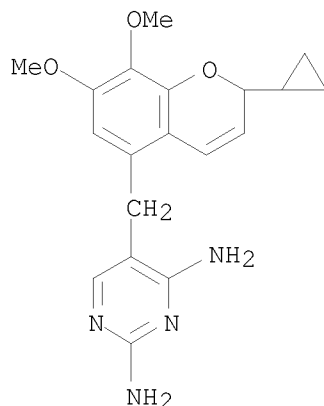
OSC.G	8	THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
RE.CNT	38	THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
		ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 31 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2007:924571 CAPLUS  
 DN 147:377512  
 TI Concentrations in plasma, epithelial lining fluid, alveolar macrophages  
 and bronchial mucosa after a single intravenous dose of 1.6 mg/kg of  
 iclaprim (AR-100) in healthy men  
 AU Andrews, J.; Honeybourne, D.; Ashby, J.; Jevons, G.; Fraise, A.; Fry, P.;  
 Warrington, S.; Hawser, S.; Wise, R.  
 CS Department of Medical Microbiology, City Hospital NHS Trust, Birmingham,  
 UK  
 SO Journal of Antimicrobial Chemotherapy (2007), 60(3), 677-680  
 CODEN: JACHDX; ISSN: 0305-7453  
 PB Oxford University Press  
 DT Journal  
 LA English  
 AB Objectives: A validated microbiol. assay was used to measure concns. of  
 iclaprim (AR-100) in plasma, bronchial mucosa (BM), alveolar macrophages  
 (AM) and epithelial lining fluid (ELF) after a single 1.6 mg/kg i.v. 60  
 min iv infusion of iclaprim. Methods: Male volunteers were randomly  
 allocated to three nominal sampling time intervals 1-2 h (Group A), 3-4 h  
 (Group B) and 5.57.0 h (Group C) after the start of the drug infusion.  
 Results: Mean iclaprim concns. in plasma, BM, AM and ELF, resp., were for  
 Group A 0.59 mg/L (SD 0.18), 0.51 mg/kg (SD 0.17), 24.51 mg/L (SD 21.22)  
 and 12.61 mg/L (SD 7.33); Group B 0.24 mg/L (SD 0.05), 0.35 mg/kg (SD  
 0.17), 7.16 mg/L (SD 1.91) and 6.38 mg/L (SD 5.17); and Group C 0.14 mg/L  
 (SD 0.05), no detectable level in BM, 5.28 mg/L (SD 2.30) and 2.66 mg/L  
 (SD 2.08). Conclusions: Iclaprim concns. in ELF and AM exceeded the MIC90  
 for penicillin-susceptible *Streptococcus pneumoniae* (MIC90 0.06 mg/L),  
 penicillin-intermediate *S. pneumoniae* (MIC90 2 mg/L), penicillin-resistant  
*S. pneumoniae* (MIC90 4 mg/L) for 7, 7 and 4 h, resp., and *Chlamydia*  
*pneumoniae* (MIC90 0.5 mg/L) for 7 h. Mean iclaprim concns. in ELF  
 exceeded the MIC90 for *Haemophilus influenzae* (MIC90 4 mg/L) and *Moraxella*  
*catarrhalis* (MIC90 8 mg/L) for up to 4 and 2 h, resp.; in AM the MIC90 was  
 exceeded for up to 7 h. Furthermore, the MIC90 for methicillin-resistant  
*Staphylococcus aureus* of 0.12 mg/L was exceeded at all sites for up to 7  
 h. These data suggest that iclaprim reaches lung concns. that should be  
 effective in the treatment of community-acquired pneumonia.  
 IT 192314-93-5, Iclaprim  
 RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU  
 (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (concns. in plasma, epithelial lining fluid, alveolar macrophages and  
 bronchial mucosa after single i.v. dose of iclaprim)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)



OSC.G 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)  
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 32 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2007:901704 CAPLUS  
 DN 147:421821  
 TI Crystal Structure of the Anthrax Drug Target, *Bacillus anthracis*  
 Dihydrofolate Reductase  
 AU Bennett, Brad C.; Xu, Hai; Simmerman, Richard F.; Lee, Richard E.;  
 Dealwis, Chris G.  
 CS Department of Biochemistry, Cellular Molecular Biology, University of  
 Tennessee, Knoxville, TN, 37996, USA  
 SO Journal of Medicinal Chemistry (2007), 50(18), 4374-4381  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 AB Spores of *Bacillus anthracis* are the infectious agent of anthrax. Current  
 antibiotic treatments are limited due to resistance and patient age  
 restrictions; thus, addnl. targets for therapeutic intervention are  
 needed. One possible candidate is dihydrofolate reductase (DHFR), a  
 biosynthetic enzyme necessary for anthrax pathogenicity. We determined the  
 crystal structure of DHFR from *B. anthracis* (baDHFR) in complex with  
 methotrexate (MTX; 1) at 2.4 Å resolution. The structure reveals the  
 crucial interactions required for MTX binding and a putative mol. basis  
 for how baDHFR has natural resistance to trimethoprim (TMP; 2). The  
 structure also allows insights for designing selective baDHFR inhibitors  
 that will have weak affinities for the human enzyme. Addnl., we have  
 found that 5-nitro-6-methylamino-isocytosine (MANIC; 3), which inhibits  
 another *B. anthracis* folate synthesis enzyme, dihydropteroate synthase  
 (DHPS), can also inhibit baDHFR. This provides a starting point for  
 designing multi-target inhibitors that are less likely to induce drug  
 resistance.  
 IT 192314-93-5D, complexes with dihydrofolate reductase  
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL  
 (Biological study)  
 (crystal structure of *Bacillus anthracis* dihydrofolate reductase)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)

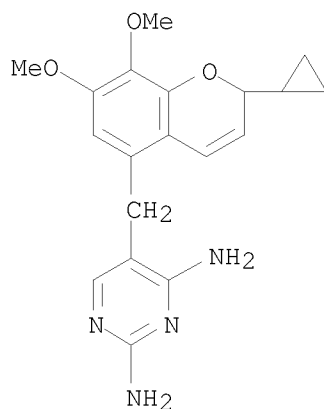


OSC.G 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)  
 RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD

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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 33 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2007:80204 CAPLUS  
 DN 146:134455  
 TI Investigational treatments for postoperative surgical site infections  
 AU Poulakou, Garyphallia; Giamarellou, Helen  
 CS University General Hospital Attikon, 4th Department of Internal Medicine,  
 National and Kapodistrian University of Athens Medical School, Athens,  
 12462, Greece  
 SO Expert Opinion on Investigational Drugs (2007), 16(2), 137-155  
 CODEN: EOIDER; ISSN: 1354-3784  
 PB Informa Healthcare  
 DT Journal; General Review  
 LA English  
 AB A review. Surgical site infections rank third among nosocomial  
 infections, representing a global threat, associated with the emergence of  
 multi-drug-resistant bacteria. The pharmaceutical industry has recently  
 curtailed developmental programs; however, the need for new compds. is  
 extremely important. This article reviews new antimicrobials and  
 immunointerventional targets for their potential to treat surgical site  
 infections in comparison with recently licensed compds. Daptomycin,  
 dalbavancin, oritavancin, telavancin, iclaprim and ranbezolid seem to be  
 promising agents against infections caused by Gram-pos. pathogens and  
 effectively address the present problems of multi-resistance in Gram-pos.  
 infections. Peptide deformylase inhibitors and immunostimulating agents  
 open new perspectives in this field; however, very few compds. targeting  
 Gram-neg. problematic pathogens are in the pipeline of the future.  
 Tigecycline (recently marketed) ceftobiprole, ceftaroline and doripenem  
 seem to possess an extended anti-Gram-pos. and -neg. spectrum. Among  
 these compds., only doripenem demonstrates activity against Pseudomonas  
 aeruginosa, for which there is a clear unmet need for new compds.,  
 focusing on new targets.  
 IT 192314-93-5, Iclaprim  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (investigational treatments for postoperative surgical site infections)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)



OSC.G 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

10/567,558

RE.CNT 157 THERE ARE 157 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



L4 ANSWER 34 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2006:847676 CAPLUS  
 DN 145:271796  
 TI Processes for the preparation of pyrimidinylmethyl 2H-chromenes  
 IN Schneider, Peter; Tahtaoui, Chouaib  
 PA Arpida AG, Switz.  
 SO PCT Int. Appl., 36 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2006087143	A1	20060824	WO 2006-EP1185	20060210
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	AU 2006215788	A1	20060824	AU 2006-215788	20060210
	CA 2596669	A1	20060824	CA 2006-2596669	20060210
	EP 1856106	A1	20071121	EP 2006-706815	20060210
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
	EE 200700051	A	20071217	EE 2007-51	20060210
	HU 2007000604	A2	20080128	HU 2007-604	20060210
	HU 2007000604	A3	20080228		
	JP 2009505943	T	20090212	JP 2007-555507	20060210
	NO 2007003701	A	20070903	NO 2007-3701	20070718
	MX 2007009282	A	20080219	MX 2007-9282	20070801
	ZA 2007006422	A	20080925	ZA 2007-6422	20070801
	ZA 2007006421	A	20081126	ZA 2007-6421	20070801
	CN 101115743	A	20080130	CN 2006-80003962	20070803
	BG 109937	A	20080530	BG 2007-109937	20070810
	BG 109938	A	20080530	BG 2007-109938	20070810
	KR 2007106635	A	20071102	KR 2007-721394	20070918
	US 20080221324	A1	20080911	US 2008-816150	20080215
PRAI	WO 2005-EP1695	A	20050218		
	WO 2000-EP2006001695	A	20050218		
	WO 2006-EP1185	W	20060210		

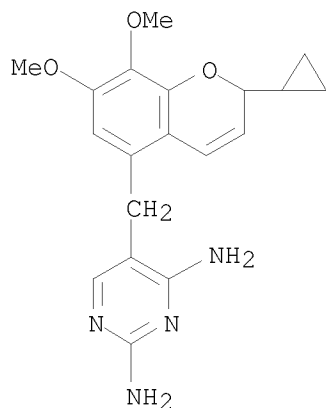
# ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS CASREACT 145:271796; MARPAT 145:271796  
 AB A process for the preparation of title compds. of formula I comprising reacting a compound of formula II [R = CMe<sub>3</sub> or CHMe<sub>2</sub>] with cyclopropyl Me ketone is disclosed. For example, I was provided in a multi-step synthesis starting from the reaction of trimethoprim with pivalic anhydride.  
 IT 192314-93-5P, 5-[(2-Cyclopropyl-7,8-dimethoxy-2H-chromen-5-yl)methyl]pyrimidine-2,4-diamine  
 RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of 5-[(2,4-diaminopyrimidinyl)methyl]-2H-chromenes and their intermediates)

RN 192314-93-5 CAPLUS

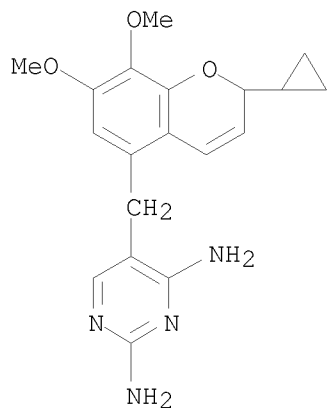
CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)  
 RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

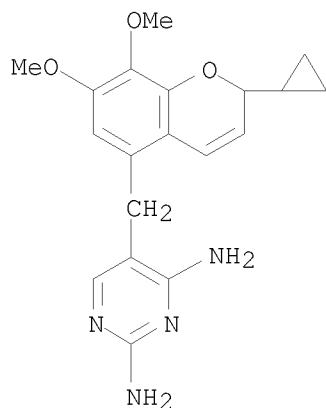
L4 ANSWER 35 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2006:621823 CAPLUS  
 DN 146:18974  
 TI Infections associated with orthopedic implants  
 AU Trampuz, Andrej; Widmer, Andreas F.  
 CS Division of Infectious Diseases and Hospital Epidemiology, University  
 Hospital, Basel, Switz.  
 SO Current Opinion in Infectious Diseases (2006), 19(4), 349-356  
 CODEN: COIDE5; ISSN: 0951-7375  
 PB Lippincott Williams & Wilkins  
 DT Journal; General Review  
 LA English  
 AB Purpose of review: We review recent advances in the prevention, diagnosis  
 and treatment of infections associated with joint prostheses and internal  
 fixation devices. Recent findings: The perioperative antimicrobial  
 prophylaxis should be administered 60-30 min before incision or before  
 inflation of the tourniquet. New diagnostic approaches include sonication  
 of removed implants to dislodge adherent microorganisms growing in  
 biofilms and the use of mol. techniques to improve diagnostic yield.  
 Treatment of implant-associated infections without removal of the device is  
 an established option for selected patients. Treatment with rifampin  
 combinations in staphylococcal infections is crucial for success. As  
 demonstrated in vitro, in animal studies and in clin. trials, quinolones  
 are suitable combination agents with rifampin against susceptible  
 staphylococci, but increasing antimicrobial resistance requires evaluation  
 of alternative combination agents, such as quinupristin-dalfopristin,  
 linezolid, and daptomycin, although clin. experience is limited. New  
 antimicrobial agents, such as dalbavancin, tigecycline, iclaprim, and  
 novel rifamycin derivs. are studied. Summary: Better understanding of the  
 interaction between microorganisms, the implant and the host may improve  
 our current approach to the diagnosis and treatment of implant-associated  
 infections. The treatment modality depends on duration of infection,  
 stability of the implant, antimicrobial susceptibility of the pathogen and  
 condition of the surrounding soft tissue.  
 IT 192314-93-5, Iclaprim  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (combinations of rifampin, quinolone, quinupristin, dalfopristin,  
 linezolid, daptomycin, dalbavancin, tigecycline, iclaprim are useful in  
 treatment of orthopedic implant-associated Staphylococcal, other bacterial  
 infections)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)

10/567,558



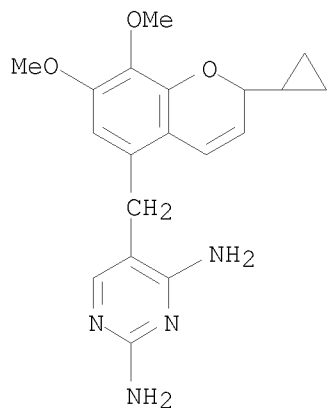
OSC.G	18	THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)
RE.CNT	79	THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT		

L4 ANSWER 36 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
AN 2006:206090 CAPLUS  
DN 144:324015  
TI Dihydrofolate reductase inhibitors as antibacterial agents  
AU Hawser, Stephen; Lociuero, Sergio; Islam, Khalid  
CS Arpida Ltd., Muenchenstein, 4142, Switz.  
SO Biochemical Pharmacology (2006) 71(7), 941-948  
CODEN: BCPA6; ISSN: 0006-2952  
PB Elsevier B.V.  
DT Journal; General Review  
LA English  
AB A review. Although only a few DHFR inhibitors have progressed as antibiotics to the market there is much renewed interest in the discovery and development of new generation DHFR inhibitors as antibacterial agents. This article describes the success in exploiting DHFR as a drugable target as exemplified by trimethoprim (TMP) and the development of several new diaminopyrimidines. Iclaprim, a recent example of a novel diaminopyrimidine currently in Phase III clin. trials, is also described together with several examples of anti-DHFR antibacterial compds. in pre-clin. development.  
IT 192314-93-5, Iclaprim  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(dihydrofolate reductase inhibitors as antibacterial agents)  
RN 192314-93-5 CAPLUS  
CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



OSC.G 51 THERE ARE 51 CAPLUS RECORDS THAT CITE THIS RECORD (51 CITINGS)  
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 37 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2005:1032155 CAPLUS  
 DN 144:141511  
 TI Recently approved and investigational antibiotics for treatment of severe  
 infections caused by Gram-positive bacteria  
 AU Appelbaum, Peter C.; Jacobs, Michael R.  
 CS Department of Pathology, Hershey Medical Center, Hershey, PA, 17033, USA  
 SO Current Opinion in Microbiology (2005), 8(5), 510-517  
 CODEN: COMIF7; ISSN: 1369-5274  
 PB Elsevier Ltd.  
 DT Journal; General Review  
 LA English  
 AB A review. The development of resistance in the major pathogenic Gram-pos.  
 genera Staphylococcus and Streptococcus has led to the need for new  
 agents that are able to overcome existing resistance mechanisms or that  
 have novel mechanisms of action. There is currently a dearth of new  
 agents that are active against resistant bacterial species. Agents that  
 have recently been approved for clin. use include linezolid, the first  
 oxazolidinone in clin. use, daptomycin, the first lipopeptide in clin.  
 use, and telithromycin, a ketolide that is derived from clarithromycin.  
 Agents currently in clin. development include tigecycline, a  
 broad-spectrum i.v. tetracycline, ceftobiprole, a broad-spectrum  
 cephalosporin that has activity against methicillin-resistant  
 staphylococci, DX-619 and WCK-771, which are potent quinolones that have  
 activity against quinolone-resistant staphylococci, oritavancin and  
 dalbavancin, both of which are new glycopeptides, and iclaprim, which is a  
 diaminopyrimidine. Addnl. agents that are in preclin. development against  
 Gram-pos. pathogens include quinoline-naphthyridine agents, which target  
 novel DNA gyrase sites, other novel quinolones that have high potency,  
 peptide deformylase inhibitors, and new lincosamide, oxazolidinone,  
 lipopeptide and cephalosporin derivs. Misuse of potent new agents will,  
 however, result in the inevitable development of resistance to these  
 agents; responsible use of potent new agents is required to prevent  
 continuation of this vicious cycle.  
 IT 192314-93-5, Iclaprim  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (diaminopyrimidine iclaprim treatment might be useful for treatment for  
 Gram pos. Staphylococcus, Streptococcus bacterial infection)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)



OSC.G	37	THERE ARE 37 CAPLUS RECORDS THAT CITE THIS RECORD (37 CITINGS)
RE.CNT	56	THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT		

L4 ANSWER 38 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2005:141063 CAPLUS  
 DN 142:240455  
 TI Novel processes and intermediates for the preparation of 2H-chromenes,  
 particularly the antibiotic iclaprim  
 IN Jaeger, Juergen; Burri, Kaspar; Greiveldinger-Poenaru, Sorana; Hoffner,  
 Johannes  
 PA Arpida A.-G., Switz.  
 SO PCT Int. Appl., 19 pp. Applicant's  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005014586	A1	20050217	WO 2003-EP8814	20030808
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	WO 2005014587	A1	20050217	WO 2004-EP8682	20040803
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1656369	A1	20060517	EP 2004-763740	20040803
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
	CN 1832942	A	20060913	CN 2004-80022787	20040803
	JP 2007501771	T	20070201	JP 2006-522311	20040803
	HU 2006000231	A2	20080428	HU 2006-231	20040803
	IN 2006CN00478	A	20070706	IN 2006-CN478	20060206
	KR 2006056375	A	20060524	KR 2006-702680	20060208
	NO 2006000643	A	20060220	NO 2006-643	20060209
	US 20080015354	A1	20080117	US 2007-567558	20070406
PRAI	WO 2003-EP8814	A	20030808		
	WO 2004-EP8682	W	20040803		

# ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS CASREACT 142:240455

AB The invention concerns a novel process for the preparation of 2H-chromenes, particularly the antibiotic (no data) iclaprim (I) and a key intermediate (II), and also two valuable intermediates in the processes. Thus, II was prepared in 4 steps from 3-hydroxy-4,5-dimethoxybenzoic acid Me ester via (1) cyclocondensation with cis-(3,3-dimethoxyprop-1-enyl)cyclopropane, (2) alkaline sapon of the ester, (3) reduction of the acid to an alc. with LiAlH4

or

Red-Al, and (4) oxidation of the alc. to an aldehyde using SO3-pyridine complex and Et3N in DMSO. Alternatively, II was prepared directly from 3-hydroxy-4,5-dimethoxybenzaldehyde and cis-(3,3-dimethoxyprop-1-enyl)cyclopropane. Condensation of II with



PhNHCH<sub>2</sub>CH<sub>2</sub>CN in DMSO in the presence of KOBu-tert gave a cis/trans mixture of PhNHCH:C(CN)R [R = (2-cyclopropyl-7,8-dimethoxy-2H-chromen-5-yl)methyl], which was cyclocondensed with guanidine HCl to give I. Advantages of the new method include use of bulk com. starting materials, avoidance of halogenated solvents, and crystalline and/or non-isolated intermediates.

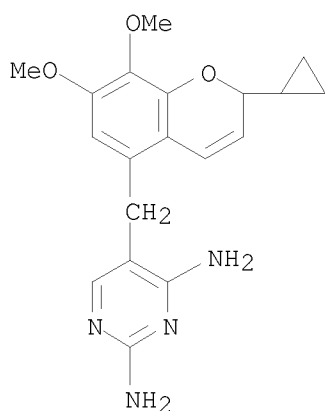
IT 192314-93-5P, Iclaprim

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(preparation of the antibiotic iclaprim and intermediates)

RN 192314-93-5 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)

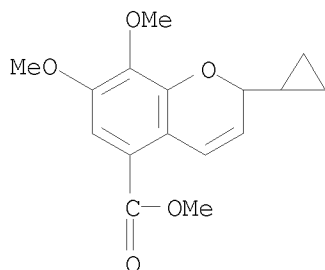


IT 192315-05-2P, 2-Cyclopropyl-7,8-dimethoxy-2H-chromene-5-carboxylic acid methyl ester 845276-37-1P, 2-Cyclopropyl-7,8-dimethoxy-2H-chromene-5-carboxylic acid 845276-38-2P, (2-Cyclopropyl-7,8-dimethoxy-2H-chromene-5-yl)methanol

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (process intermediate; preparation of the antibiotic iclaprim and intermediates)

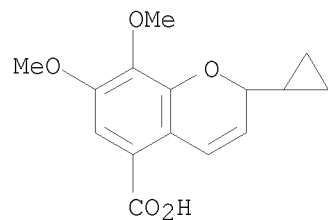
RN 192315-05-2 CAPLUS

CN 2H-1-Benzopyran-5-carboxylic acid, 2-cyclopropyl-7,8-dimethoxy-, methyl ester (CA INDEX NAME)

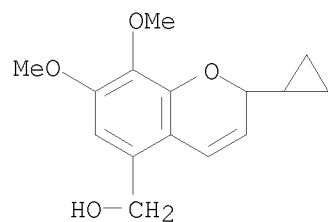


10/567,558

RN 845276-37-1 CAPLUS  
CN 2H-1-Benzopyran-5-carboxylic acid, 2-cyclopropyl-7,8-dimethoxy- (CA INDEX NAME)

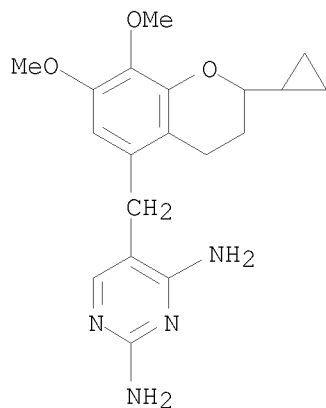


RN 845276-38-2 CAPLUS  
CN 2H-1-Benzopyran-5-methanol, 2-cyclopropyl-7,8-dimethoxy- (CA INDEX NAME)



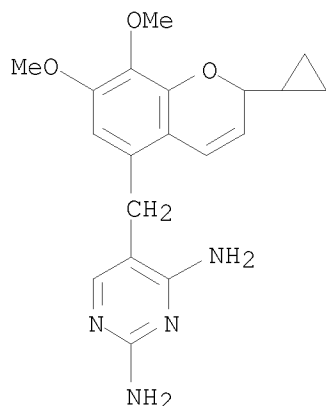
OSC.G 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)  
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 39 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2004:566933 CAPLUS  
 DN 141:270985  
 TI Three-Dimensional Quantitative Structure-Activity Relationship Analysis of  
 a Set of Plasmodium falciparum Dihydrofolate Reductase Inhibitors Using a  
 Pharmacophore Generation Approach  
 AU Parenti, Marco Daniele; Pacchioni, Sara; Ferrari, Anna Maria; Rastelli,  
 Giulio  
 CS Dipartimento di Scienze Farmaceutiche, Universita di Modena e Reggio  
 Emilia, Modena, 41100, Italy  
 SO Journal of Medicinal Chemistry (2004) 47(17), 4258-4267  
 CODEN: JMCMAR; ISSN: 0022-2625  
 PB American Chemical Society  
 DT Journal  
 LA English  
 AB A 3D pharmacophore model able to quant. predict inhibition consts. was  
 derived for a series of inhibitors of Plasmodium falciparum dihydrofolate  
 reductase (PfDHFR), a validated target for antimalarial therapy. The data  
 set included 52 inhibitors, with 23 of these comprising the training set  
 and 29 an external test set. The activity range, expressed as  $K_i$ , of the  
 training set mols. was from 0.3 to 11 300 nM. The 3D pharmacophore,  
 generated with the HypoGen module of Catalyst 4.7, consisted of two  
 hydrogen bond donors, one pos. ionizable feature, one hydrophobic aliphatic  
 feature, and one hydrophobic aromatic feature and provided a 3D-QSAR model  
 with a correlation coefficient of 0.954. Importantly, the type and spatial  
 location of the chemical features encoded in the pharmacophore were in full  
 agreement with the key binding interactions of PfDHFR inhibitors as  
 previously established by mol. modeling and crystallog. of  
 enzyme-inhibitor complexes. The model was validated using several  
 techniques, namely, Fisher's randomization test using CatScramble,  
 leave-one-out test to ensure that the QSAR model is not strictly dependent  
 on one particular compound of the training set, and activity prediction in  
 an external test set of compds. In addition, the pharmacophore was able to  
 correctly classify as active and inactive the dihydrofolate reductase and  
 aldose reductase inhibitors extracted from the MDDR database, resp. This test  
 was performed to challenge the predictive ability of the pharmacophore  
 with two classes of inhibitors that target very different binding sites.  
 Mol. diversity of the data sets was finally estimated by the Tanimoto  
 approach. The results obtained provide confidence for the utility of the  
 pharmacophore in the virtual screening of libraries and databases of  
 compds. to discover novel PfDHFR inhibitors.  
 IT 756887-17-9  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (QSAR of Plasmodium falciparum dihydrofolate reductase inhibitors using  
 pharmacophore generation approach)  
 RN 756887-17-9 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-3,4-dihydro-7,8-dimethoxy-2H-1-  
 benzopyran-5-yl)methyl]- (CA INDEX NAME)



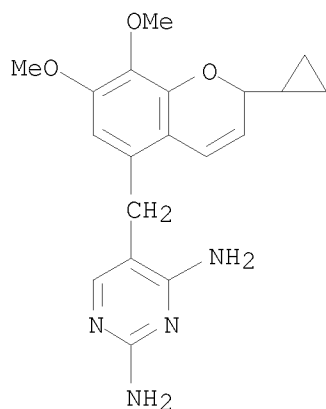
OSC.G	22	THERE ARE 22 CAPLUS RECORDS THAT CITE THIS RECORD (22 CITINGS)
RE.CNT	35	THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
		ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 40 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2004:375664 CAPLUS  
 DN 141:85429  
 TI In vitro activity of a novel diaminopyrimidine compound, iclaprim, against  
 Chlamydia trachomatis and C. pneumoniae  
 AU Kohlhoff, S. A.; Roblin, P. M.; Reznik, T.; Hawser, S.; Islam, K.;  
 Hammerschlag, M. R.  
 CS Dep. Pediatrics, Downstate Medical Center, State Univ. New York, Brooklyn,  
 NY, 11203-2098, USA  
 SO Antimicrobial Agents and Chemotherapy (2004), 48(5), 1885-1886  
 CODEN: AMACCQ; ISSN: 0066-4804  
 PB American Society for Microbiology  
 DT Journal  
 LA English  
 AB The in vitro activities of iclaprim, a novel dihydrofolate reductase  
 inhibitor, azithromycin, and levofloxacin were tested against 10 strains  
 of C. trachomatis and 10 isolates of Chlamydia pneumoniae. For C.  
 trachomatis and C. pneumoniae, the iclaprim MIC and minimal bactericidal  
 concentration at which 90% of isolates were inhibited (MIC90 and MBC90) were  
 0.5  $\mu\text{g/mL}$ , compared to an azithromycin MIC90 and MBC90 of 0.125  $\mu\text{g/mL}$   
 and levofloxacin MIC90s and MBC90s of 1  $\mu\text{g/mL}$  for C. trachomatis and  
 0.5  $\mu\text{g/mL}$  for C. pneumoniae.  
 IT 192314-93-5, Iclaprim  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (in vitro activity of iclaprim against Chlamydia trachomatis and C.  
 pneumoniae)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
 yl)methyl]- (CA INDEX NAME)



OSC.G 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)  
 RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 41 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2004:373800 CAPLUS  
 DN 141:166971  
 TI Iclaprim: Antibacterial dihydrofolate reductase inhibitor  
 AU Sorbera, L. A.; Castaner, J.; Rabasseda, X.  
 CS Prous Science, Barcelona, 08080, Spain  
 SO Drugs of the Future (2004), 29(3), 220-225  
 CODEN: DRFUD4; ISSN: 0377-8282  
 PB Prous Science  
 DT Journal; General Review  
 LA English  
 AB A review. The need for potent antibacterial agents with novel mechanisms of action remains a research priority. Dihydrofolate reductase (DHFR) is an enzyme essential for bacterial survival that is an excellent target for antibacterial drug development. Diaminopyrimidines such as trimethoprim (TMP) are inhibitors of DHFR which have been used clin. as monotherapy and in combination with other agents with relative success. However, TMP is weakly bactericidal and resistance has emerged due to frequent use. Researchers have therefore focused on the discovery of synthetic derivs. of benzyldiaminopyrimidines which exhibit improved potency and selectivity and can overcome resistance. Iclaprim (I) is a novel diaminopyrimidine that has shown potent, expanded-spectrum activity against Gram-pos. bacteria including methicillin-resistant *Staphylococcus aureus*, vancomycin-intermediate and vancomycin-resistant *S. aureus* and macrolide-, quinolone- and TMP-resistant strains. Activity was also observed against Gram-pos. and Gram-neg. pathogens involved in respiratory tract infections and it proved effective in animal models of infection. Moreover, in a phase II trial, I was shown to be safe and effective as a treatment for complicated skin and soft tissue infections.  
 IT 192314-93-5P, Iclaprim  
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (antibacterial activity of the dihydrofolate reductase inhibitor iclaprim)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



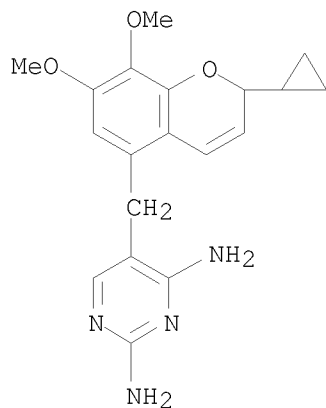
OSC.G 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)

10/567,558

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

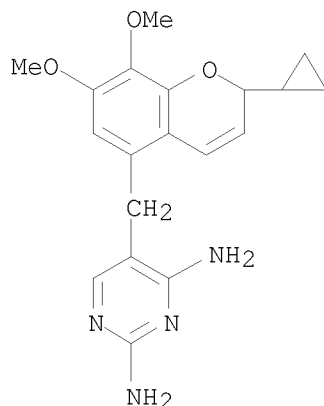
L4 ANSWER 42 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
AN 2004:54705 CAPLUS  
DN 140:232383  
TI Vancomycin-resistant Staphylococcus aureus isolate from a patient in  
Pennsylvania  
AU Tenover, Fred C.; Weigel, Linda M.; Appelbaum, Peter C.; McDougal, Linda  
K.; Chaitram, Jasmine; McAllister, Sigrid; Clark, Nancye; Killgore,  
George; O'Hara, Caroline M.; Jevitt, Laura; Patel, Jean B.; Bozdogan,  
Buelent  
CS Division of Healthcare Quality Promotion, Centers for Disease Control and  
Prevention, Atlanta, GA, 30333, USA  
SO Antimicrobial Agents and Chemotherapy (2004), 48(1), 275-280  
CODEN: AMACCQ; ISSN: 0066-4804  
PB American Society for Microbiology  
DT Journal  
LA English  
AB A vancomycin-resistant Staphylococcus aureus (VRSA) isolate was obtained  
from a patient in Pennsylvania in Sept. 2002. Species identification was  
confirmed by standard biochem. tests and anal. of 16S ribosomal DNA, gyrA, and  
gyrB sequences; all of the results were consistent with the S. aureus  
identification. The MICs of a variety of antimicrobial agents were determined  
by broth microdilution and macrodilution methods following National  
Committee for Clin. Laboratory Stds. (NCCLS) guidelines. The isolate was  
resistant to vancomycin (MIC = 32 µg/mL), aminoglycosides,  
β-lactams, fluoroquinolones, macrolides, and tetracycline, but it was  
susceptible to linezolid, minocycline, quinupristin-dalfopristin,  
rifampin, teicoplanin, and trimethoprim-sulfamethoxazole. The isolate,  
which was originally detected by using disk diffusion and a vancomycin  
agar screen plate, was vancomycin susceptible by automated susceptibility  
testing methods. Pulsed-field gel electrophoresis (PFGE) of SmaI-digested  
genomic DNA indicated that the isolate belonged to the USA100 lineage  
(also known as the New York/Japan clone), the most common staphylococcal  
PFGE type found in hospitals in the United States. The VRSA isolate  
contained two plasmids of 120 and 4 kb and was pos. for mecA and vanA by  
PCR amplification. The vanA sequence was identical to the vanA sequence  
present in Tn1546. A DNA probe for vanA hybridized to the 120-kb plasmid.  
This is the second VRSA isolate reported in the United States.  
IT 192314-93-5, Iclaprim  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(vancomycin-resistant Staphylococcus aureus isolate from patient in  
Pennsylvania)  
RN 192314-93-5 CAPLUS  
CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-  
yl)methyl]- (CA INDEX NAME)





OSC.G	161	THERE ARE 161 CAPLUS RECORDS THAT CITE THIS RECORD (161 CITINGS)
RE.CNT	39	THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
		ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 43 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2003:883789 CAPLUS  
 DN 141:20308  
 TI Antibacterial susceptibility of a vancomycin-resistant *Staphylococcus aureus* strain isolated at the Hershey Medical Center  
 AU Bozdogan, Buelent; Esel, Duygu; Whitener, Cynthia; Browne, Frederick A.; Appelbaum, Peter C.  
 CS Department of Pathology, Hershey Medical Center, Hershey, PA, 17033, USA  
 SO Journal of Antimicrobial Chemotherapy (2003) 52(5), 864-868  
 CODEN: JACHDX; ISSN: 0305-7453  
 PB Oxford University Press  
 DT Journal  
 LA English  
 AB *Staphylococcus aureus* strain HMC3 isolated at the Hershey Medical Center, was resistant to vancomycin (VRSA) through the presence of the *vanA* resistance gene; it also contained *mecA*, *erm(A)*, *erm(B)*, *tet(K)* and *aac(6')-aph(2'')*, conferring resistance to licensed  $\beta$ -lactams, macrolides, tetracycline and aminoglycosides. HMC3 also had alterations in *GyrA* and *GrlB* and was resistant to available quinolones. Exptl. drugs with low MICs (<2 mg/L) for VRSA HMC3 included cephalosporins BAL9141 and RWJ-54428; glycopeptides oritavancin and dalbavancin; the lipopeptide daptomycin; the glycolipodepsipeptide ramoplanin; new fluoroquinolones WCK 771 A, WCK 1153, DK-507k and sitafloxacin; and the DNA nanobinder GS02-02. These agents were all bactericidal as were trimethoprim/sulfamethoxazole and teicoplanin (MIC 4 mg/L). Oxazolidinones linezolid and ranbezolid; the injectable streptogramin quinupristin/dalfopristin; DNA nanobinders GS2-10547 and GS02-104; peptide deformylase inhibitors NVP-PDF713 and GS02-12; tetracycline derivative tigecycline; the antifolate iclaprim; mupirocin and fusidic acid were all active in vitro but bacteriostatic.  
 IT 192314-93-5, Iclaprim  
 RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (antibacterial susceptibility of a vancomycin-resistant *Staphylococcus aureus* strain isolated at the Hershey Medical Center)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)

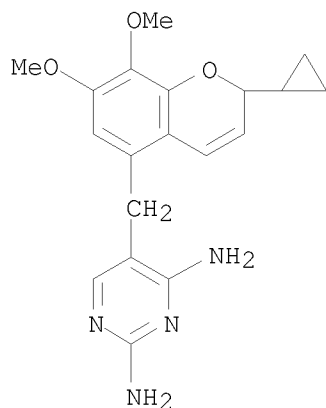


OSC.G 109 THERE ARE 109 CAPLUS RECORDS THAT CITE THIS RECORD (109 CITINGS)  
 RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD

10/567,558

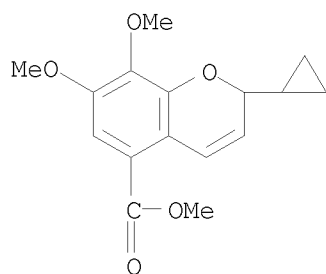
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 44 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2003:877316 CAPLUS  
 DN 140:122159  
 TI Iclaprim, a novel diaminopyrimidine with potent activity on trimethoprim sensitive and resistant bacteria  
 AU Schneider, Peter; Hawser, Stephen; Islam, Khalid  
 CS Arpida Ltd., Muenchenstein, CH-4142, Switz.  
 SO Bioorganic & Medicinal Chemistry Letters (2003), 13(23), 4217-4221  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 AB Iclaprim, a new selective dihydrofolate inhibitor was synthesized based on rational drug design. Iclaprim's interaction with a resistant Staphylococcus aureus dihydrofolate reductase (DHFR) is outlined in comparison to trimethoprim (TMP). This compound is active against methicillin, TMP and vancomycin resistant strains. Arpida Ltd. is developing Iclaprim for serious hospital infections from Gram-pos. pathogens and respiratory tract infections.  
 IT 192314-93-5, Iclaprim  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (Iclaprim, a novel diaminopyrimidine with potent activity on trimethoprim sensitive and resistant bacteria)  
 RN 192314-93-5 CAPLUS  
 CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



OSC.G 52 THERE ARE 52 CAPLUS RECORDS THAT CITE THIS RECORD (53 CITINGS)  
 RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

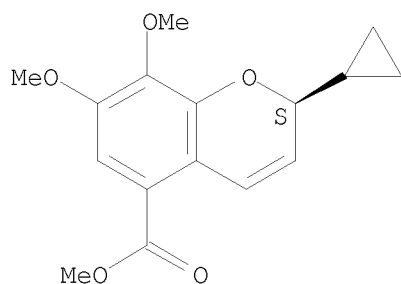
L4 ANSWER 45 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2003:827746 CAPLUS  
 DN 140:59491  
 TI Pt(IV)-catalyzed cyclization of arene-alkyne substrates via C-H bond functionalization  
 AU Pastine, Stefan J.; Youn, So Won; Sames, Dalibor  
 CS Department of Chemistry, Columbia University, New York, NY, 10027, USA  
 SO Tetrahedron (2003), 59(45), 8859-8868  
 CODEN: TETRAE; ISSN: 0040-4020  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 OS CASREACT 140:59491  
 AB PtCl<sub>4</sub> was proven to be a hydroarylation catalyst with an efficiency and substrate scope superior to previously reported methods. This catalyst showed consistent performance with arene-yne substrates of diverse structural features, including propargyl ethers, propargylamines, and alkynoate esters, providing good to excellent yields of the 6-endo products, chromenes, e.g., I, dihydroquinolines, e.g., II, and coumarins, e.g., III. Pt(II), Pd(II), and Ga(III) salts were shown to be sensitive to the substitution on the alkyne moiety. PtCl<sub>4</sub> is compatible with both terminal and disubstituted alkynes, as well as with various functionalities on the arene ring, including Me, methoxy, hydroxy, protected amine, and halide.  
 IT 192315-05-2P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of chromenes via platinum-catalyzed intramol. cyclization of aryloxyalkynes)  
 RN 192315-05-2 CAPLUS  
 CN 2H-1-Benzopyran-5-carboxylic acid, 2-cyclopropyl-7,8-dimethoxy-, methyl ester (CA INDEX NAME)



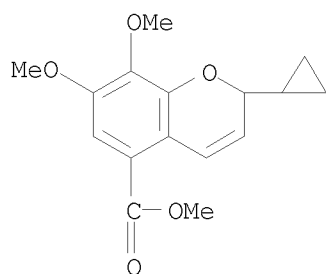
OSC.G 68 THERE ARE 68 CAPLUS RECORDS THAT CITE THIS RECORD (69 CITINGS)  
 RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 46 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 1999:381749 CAPLUS  
 DN 131:144499  
 TI Enantioselective synthesis and photoracemization studies of  
 (+)-2-cyclopropyl-7,8-dimethoxy-2H-chromene-5-carboxylic acid methyl  
 ester, an advanced intermediate of a dihydrofolate reductase inhibitor  
 AU Wipf, Peter; Weiner, Warren S.  
 CS Department of Chemistry, University of Pittsburgh, Pittsburgh, PA, 15260,  
 USA  
 SO Journal of Organic Chemistry (1999), 64(14), 5321-5324  
 CODEN: JOCEAH; ISSN: 0022-3263  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 131:144499  
 AB In a formal asym. synthesis of the potent dihydrofolate reductase  
 inhibitor cyclopropyl(pyrimidinylmethyl)benzopyran I, the enantioenriched  
 building block cyclopropylbenzopyran (S)-II was obtained in 7 steps and in  
 21% overall yield from 3-hydroxy-4,5-dimethoxybenzoic acid. A caveat in  
 the preparation and pharmaceutical use of chromenes of type II is their  
 surprisingly facile photoracemization at the stereocenter next to the  
 chromene oxygen. The half-lives for racemization of a solution of II in a  
 pyrex flask can be as short as 16 h. This is the first kinetic anal. of  
 chromene photo-racemization.  
 IT 236393-00-3P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (enantioselective synthesis and photoracemization of  
 cyclopropylchromenecarboxylate)  
 RN 236393-00-3 CAPLUS  
 CN 2H-1-Benzopyran-5-carboxylic acid, 2-cyclopropyl-7,8-dimethoxy-, methyl  
 ester, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 192315-05-2P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (enantioselective synthesis and photoracemization of  
 cyclopropylchromenecarboxylate)  
 RN 192315-05-2 CAPLUS  
 CN 2H-1-Benzopyran-5-carboxylic acid, 2-cyclopropyl-7,8-dimethoxy-, methyl  
 ester (CA INDEX NAME)

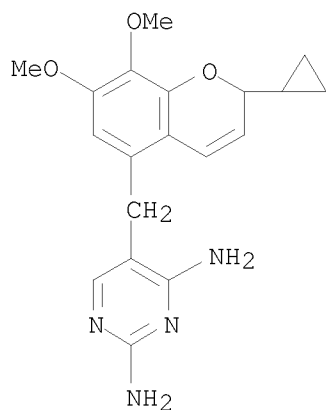


IT 192314-93-5P

RL: PNU (Preparation, unclassified); PREP (Preparation)  
(enantioselective synthesis of cyclopropylchromenecarboxylate and  
formal synthesis of (aminopyrimidinylmethyl)cyclopropylchromene  
dihydrofolate reductase inhibitor)

RN 192314-93-5 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



OSC.G 47 THERE ARE 47 CAPLUS RECORDS THAT CITE THIS RECORD (48 CITINGS)  
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 47 OF 47 CAPLUS COPYRIGHT 2010 ACS on STN

AN 1997:479370 CAPLUS

DN 127:108943

OREF 127:21015a

TI Preparation of 5-(2,4-diaminopyrimidin-5-ylmethyl)-2H-1-benzopyranes as antibacterials

IN Masciadri, Raffaello

PA F. Hoffmann-La Roche Ag, Switz.

SO PCT Int. Appl., 25 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9720839	A1	19970612	WO 1996-EP5151	19961122
	W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2238521	A1	19970612	CA 1996-2238521	19961122
	CA 2238521	C	20050816		
	AU 9676963	A	19970627	AU 1996-76963	19961122
	AU 708578	B2	19990805		
	EP 866791	A1	19980930	EP 1996-939890	19961122
	EP 866791	B1	20020130		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	CN 1203600	A	19981230	CN 1996-198783	19961122
	CN 1092194	C	20021009		
	BR 9611871	A	19990217	BR 1996-11871	19961122
	JP 2000501399	T	20000208	JP 1997-520925	19961122
	JP 3309340	B2	20020729		
	EP 1149834	A1	20011031	EP 2001-117420	19961122
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	AT 212629	T	20020215	AT 1996-939890	19961122
	PT 866791	E	20020531	PT 1996-939890	19961122
	ES 2169272	T3	20020701	ES 1996-939890	19961122
	US 5773446	A	19980630	US 1996-758993	19961202
PRAI	CH 1995-3425	A	19951204	cited in DS	
	EP 1996-939890	A3	19961122		
	WO 1996-EP5151	W	19961122		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS MARPAT 127:108943

AB The title compds. [I; R1 = straight-chain C5-10-alkyl, branched C3-5-alkyl, C3-6-cycloalkyl, C3-5- $\omega$ -carboxyalkyl; R2, R3 = C1-5-alkyl; R1 = H; R2 = C3-5- $\omega$ -alkyl] and their pharmaceutically acceptable acid addition salts which have antibiotic properties and can be used in the control or prevention of infectious diseases, were prepared and formulated. Thus, treatment of guanidine.HCl with tert-BuOK in EtOH followed by addition of (RS)-3-anilino-2-(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-ylmethyl)acrylonitrile afforded I [R1 = cyclopropyl; R2, R3 = MeO]. Compound I [R1 = iPr; R2, R3 = MeO] showed IC<sub>50</sub> of 0.001  $\mu$ M against the purified DHFR of the reference strain S. aureus ATCC25923.

IT 192314-93-5P

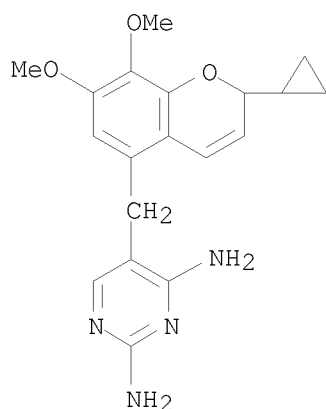
RL: BAC (Biological activity or effector, except adverse); BSU (Biological



study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);  
 BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of 5-(2,4-diaminopyrimidin-5-ylmethyl)-2H-1-benzopyranes as  
 antibacterials)

RN 192314-93-5 CAPLUS

CN 2,4-Pyrimidinediamine, 5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]- (CA INDEX NAME)



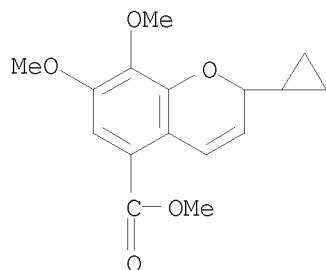
IT 192315-05-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)

(preparation of 5-(2,4-diaminopyrimidin-5-ylmethyl)-2H-1-benzopyranes as  
 antibacterials)

RN 192315-05-2 CAPLUS

CN 2H-1-Benzopyran-5-carboxylic acid, 2-cyclopropyl-7,8-dimethoxy-, methyl  
 ester (CA INDEX NAME)



OSC.G 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)  
 RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/567,558

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COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

274.57

466.82

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE

TOTAL

ENTRY

SESSION

CA SUBSCRIBER PRICE

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-39.95

STN INTERNATIONAL LOGOFF AT 16:39:12 ON 27 MAR 2010